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(54) **Coated omeprazole tablets**

(57) Pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating is useful in the treatment of gastrointestinal diseases.

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This print embodies corrections made under Section 117(1) of the Patents Act 1977.

SPECIFICATION

New pharmaceutical preparation for oral use

Field of the invention

The present invention is related to a new stable pharmaceutical preparation containing omeprazole for oral use, to a method for the manufacture of such a preparation and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

Background of the invention

From e.g. EP-A1-0 005 129 omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, a potent inhibitor of gastric acid secretion is known. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov 27, 1982, p. 1223-1224) and can be used for the treatment of gastric and duodenal ulcers. Omeprazole is however susceptible to degradation/transformation in acid reacting and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture and organic solvents.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

In human pharmacological studies it was found that the rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole to the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; *20* (suppl 108) p. 113-120). A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal.

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

An enteric coated dosage form of omeprazole was reported by Pilbrant and Cederberg, in the above cited Scand. J. Gastroenterology 1985; *20* (suppl 108) p. 113-120. The publication describes a conventional enteric coated dosage form and states that it has an acceptable storage stability - for clinical studies. It was later found that the stability of this dosage form was insufficient during long-term storage required for a marketed pharmaceutical dosage form.

If a conventional formulation of omeprazole is made, the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

In DE-A1-3046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of omeprazole in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing omeprazole since direct contact between substances such as cellulose acetate phthalate (CAP) and omeprazole causes degradation and discoloration of omeprazole.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of omeprazole in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating.

Both this preparation and the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for omeprazole, where a rapid release of the drug in the small intestine is needed.

DE-A1 12 04 363 describes coating with three layers to achieve release of drug in the ileum, an aim which is outside the scope of the present invention.

GB-A-1 485 676 describes a way to obtain a preparation, which effervesces in the small intestine, by enteric coating a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing omeprazole, as the presence of an acid in contact with omeprazole in the cores should give as a result that omeprazole was degraded.

Outline of the invention

The object of the present invention is to provide an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing omeprazole mixed with alkaline compounds or an alkaline salt of omeprazole optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to bring down the water content to a very low level in order to obtain a good stability of the dosage form during long-term storage.

Detailed description of the invention

Cores

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$,$(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trishydroxyimethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of omeprazole such as the sodium, potassium, magnesium, calcium etc. salts of omeprazole, which are described in e.g. EP-A2-124 495, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, tablets, hard gelatine or soft gelatine capsules by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from he outside in towards the alkaline core can react with hydroxyl ions diffusing from the inside out towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3,4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyvinyl acetal diethylaminoacetate or the like.

The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit® L 12,5 or Eudragit® L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing omeprazole mixed with an alkaline reacting compound or cores containing an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound. The alkaline reacting core material and/or alkaline salt of the active ingredient, omeprazole, enhance the stability of omeprazole. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and/or the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing omeprazole (enteric coated tablets, capsules or pellets) is kept low, preferably not more than 1.5% by weight. As a consequence the final package containing hard gelatin capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the gelatin sheel to a level where the water content of the enteric coated pellets filled in the capsules is not more than 1.5% by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and the disease. In general the daily dose will be in the range of 1-400 mg of omeprazole. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

The effect of different magnesium compounds was evaluated in the form of enteric coated tablets. Tablet cores were first made by known techniques according to the formulations listed in Table 1, followed by application of separating layers and enteric coating layers as shown in Table 2.

Table 1 Formulations for the tablet cores (mg)

Formulations No.	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Omeprazole	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Lactose	134.0	119.0	119.0	119.0	118.8	118.5	119.0
Hydroxypropyl cellulose (low substitution)	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropyl cellulose	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Na_2HPO_4	-	15.0	-	-	0.2	-	-
Na lauryl sulfate	-	-	-	-	-	0.5	-
MgO	-	-	15.0	-	-	-	-
$Mg(OH)_2$	-	-	-	15.0	15.0	15.0	-
Synthetic hydrotalcite $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O]$	-	-	-	-	-	-	15.0
Total	160.0	160.0	160.0	160.0	160.0	160.0	160.0

Table 2 Formulations for coatings (mg)

Formulation No.	*I*	*II*	*III*	*IV*
Separating layer (inner):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Magnesium hydroxide	-	-	0.3	-
Synthetic hydrotalcite	-	-	-	0.3
Separating layer (outer):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Enteric coating layer:				
Hydroxypropyl methylcellulose phthalate	7.0	7.0	7.0	7.0
Cetyl alcohol	0.5	0.5	0.5	0.5

The tablets thus obtained were stored in open form under so called accelerated conditions, that is 40°C, and 75 % relative humidity, and the changes in appearance with the passage of time were observed. Storage for six months under these conditions corresponds to storage at normal temperature for three years. This means that high stability sufficient for practical use may be assured if a drug remains intact for about one week under the mentioned conditions. The result is summarized in Table 3. As may be seen from the table, a remarkable stabilizing effect is achieved when a magnesium compound is contained in the inner separating layer.

Table 3 Stabilizing effect (appearance of preparations)

Coating Layer		Core material 1	2	3	4	5	6	7
I	At the start	C	A	A	A	A	A	A
	60°C; after 7 days	E	D	C	C	C	C	D
	40°C; 75%RH; after 7 days	F	E	B	B	B	B	E
II	At the start	A	A	A	A	A	A	A
	60°C; after 7 days	E	B	A	A	A	A	C
	40°C; 75%RH; after 7 days	E	D	A	A	A	A	D
III	At the start	A	A	A	A	A	A	A
	60°C; after 15 days	B	A	A	A	A	A	A
	40°C; after 30 days	A	A	A	A	A	A	A
	40°C; 75%RH; after 15 days	B	A	A	A	A	A	A
IV	At the start	A	A	A	A	A	A	A
	60°C; after 15 days	B	A	A	A	A	A	A
	40°C; after 30 days	A	A	A	A	A	A	A
	40°C; 75%RH; after 15 days	B	A	A	A	A	A	A

A: white, B: brownish white, C: faint brown, D: light brown, E: brown, F: deep brown.

All the samples evaluated as A (white) in the above table showed no discoloration even on split surfaces. The samples evaluated as B (brownish white) showed little change in appearance, but some discoloration was observed on split surfaces.

Table 4 shows the result of a stability test on the omeprazole preparation according to Example 1 (Formulation No 4-IV). The formulation was stored in a closed glass bottle at room temperature for the indicated period of time. This clearly demonstrates that preparations with unusually high stability were obtained.

Table 4 Stability of enteric coated omeprazole preparations (Tablets of Formulation No. 4-IV)

Storage Period	Appearance	Omeprazole Content (%)
At the start of test	White	100.0
1 year at room temperature	White	99.9
2 years at room temperature	White	100.0

Example 2

Uncoated pellets

I	Mannitol powder	16150 g
	Lactose anhydrous	800 g
	Hydroxypropyl cellulose	600 g
	Microcrystalline cellulose	400 g
II	Omeprazole	2000 g
	Sodium lauryl sulphate	50 g
	Disodium hydrogen phosphate	80 g
	Distilled water	4400 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

III	Uncoated omeprazole pellets	6000 g
	Hydroxypropyl methylcellulose	240 g
	Distilled water	4800 g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric-coated pellets

	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
IV	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 225 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

Example 3

This example illustrates that a variety of polymers can be used for subcoating, e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols.

Uncoated pellets

	Mannitol powder	1620 g
	Lactose anhydrous	80 g
I	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
	Omeprazole	200 g
	Sodium lauryl sulphate	1.0 g
II	Disodium hydrogen phosphate	9.3 g
	Distilled water	515 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

	Uncoated omeprazole pellets	500 g
III	Polyvinylpyrrolidone	20 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric-coated pellets

	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	45 g
IV	Cetyl alcohol	5 g
	Acetone	219 g
	Ethanol	680 g

The enteric-coated pellets were prepared as described in Example 2.

Example 4
Uncoated pellets

I	Mannitol powder	1610 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Pluronic F68	10 g
	Disodium hydrogen phosphate	24 g
	Distilled water	450 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

III	Uncoated pellets	500 g
	Polyvinylpyrrolidone	30 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric coated pellets

IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The enteric coated pellets were prepared as described in Example 2.

Example 5

This example illustrates that a variety of of polymers can be used as enteric coating material e.g. cellulose acetate phthalate, poly-(vinyl acetate/vinyl alcohol phthalate), hydroxypropyl methylcellulose phthalate, poly-(methacrylic acid/ methacrylic acid methyl esters), poly-(acrylic acid/methacrylic acid methyl esters). The polymers can be applied with/without plasticizer, e.g., polyethylene glycols, triacetin, dimethyl polysiloxan, Citroflex®, cetyl alcohol, stearyl alcohol, diethyl phthalate.

Enteric-coated pellets can also be manufactured from water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit®L 100-55, Coating CE 5142 (BASF).

Uncoated pellets

I	Lactose powder	277 g
	Lactose anhydrous	118 g
	Hydroxypropyl cellulose	25 g
	Colloidal silica	25 g
II	Omeprazole	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	2 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	170 g

The uncoated pellets were prepared as described above.

Subcoated pellets

The uncoated pellets were subcoated as described in Example 2.

Enteric coated pellets

III	Subcoated pellets	500 g
	Eudragit L 100	45 g
	Stearyl alcohol	4.5 g
	Ethanol	1320 g

The enteric coated pellets were prepared as described above.

Example 6

Formulations with the sodium salt of omeprazole.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 2 with the exception that the omeprazole sodium salt was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g
	Pellets subcoated with III	500 g
IV	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500 g
V	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 2.

Examples 7 and 8

Formulations with the magnesium salt of omeprazole.

Uncoated pellets

		Example No 7	8
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1673 g	1473 g
	Microcrystalline cellulose	100 g	100 g
II	Magnesium hydroxide	-	200 g
	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole magnesium salt was added together with the other ingredients in mixture I.

Subcoated pellets

		Examples 7 and 8
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

Enteric coated pellets

		Examples 7 and 8
	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
IV	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Examples 9 and 10
Manufacture of tablets.

Tablet cores

		Examples No 9	10
	Omeprazole	400 g	-
I	Omeprazole sodium salt, corresponding to omeprazole 400 g	-	426 g
	Lactose, anhydrous	1420 g	1409 g
	Polyvinylpyrrolidone, crosslinked	100 g	100 g
	Sodium carbonate, anhydrous	15 g	-
II	Methyl cellulose	12 g	12 g
	Distilled water	200 g	200 g
	Magnesium stearate	30 g	30 g

The powder mixture I was carefully homogenized and granulated by the solution II. The wet mass was dried in a fluidized bed dryer using an inlet air temperature of +50°C for 30 minutes. The dried mixture was then forced through a sieve with an aperture of 0.5 mm. After mixing with magnesium stearate the granulate was tableted on a tableting machine using 6 mm punches. The tablet weight was 100 mg.

Subcoating
The tablets containing omeprazole were subcoated with approximately 10 % by weight of hydroxypropyl methylcellulose from a water solution using a perforated coating pan apparatus.

The tablets containing omeprazole sodium salt were subcoated using the dry coating technique. A tablet granulate containing

Lactose anhydrous	4000 g
Polyvinylpyrrolidone, (PVP)	180 g
Ethanol 95 %	420 g
Magnesium stearate	42 g

was prepared in the following way. The lactose was granulated with a solution of PVP in ethanol and dried. After drying magnesium stearate was admixed.

The granulate mass was dry coated around the tablet cores of example 9 using a Manesty Dry Cota® tableting machine. The tablet weight of the dry coated tablets was 475 mg. Each tablet contained 20 mg of omeprazole.

Enteric coating

The subcoated tablets obtained above were enteric coated using the same coating solution:

Hydroxypropyl methylcellulose phthalate	1500 g
Cetyl alcohol	105 g
Methylene chloride	15000 g
Isopropanol	15000 g
Distilled water	3150 g

The coating was applied in a perforated coating pan apparatus. An approximate amount of one kg of coating solution was applied for each kg of tablets.

Comparative Examples

Examples I, II and III

These examples illustrate that the buffer salt used effects the enteric-coated omeprazole pellet properties when the sub-coating layer is absent. A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellet shows inferior acid resistance properties. Cf also the Example 4 above.

Uncoated pellets

		Examples No		
		I	II	III
I	Mannitol powder	1610 g	1610 g	1610 g
	Lactose anhydrous	80 g	80 g	80 g
	Hydroxypropyl cellulose	60 g	60 g	60 g
	Microcrystalline cellulose	40 g	40 g	40 g
II	Omeprazole	200 g	200 g	200 g
	Pluronic F68	10 g	10 g	10 g
	Disodium hydrogen phosphate	2 g	8 g	24 g
	Distilled water	450 g	450 g	450 g

The uncoated pellets were prepared as described in Example 2 above.

Enteric coated pellets

III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The coated pellets were prepared as described in Example 2 above.

Example IV

This formulation is the same as in Example 6 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 6.

Enteric-coated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example V

This formulation is the same as in Example 8 above, but no subcoating layer was used.

Uncoated pellets

	Omeprazole magnesium salt	222 g
	Mannitol powder	1473 g
I	Microcrystalline cellulose	100 g
	Magnesium hydroxide	200 g
II	Sodium lauryl sulphate	5 g
	Distilled water	375 g

The preparation was made as described in Example 8.

Enteric coated pellets

	Uncoated pellets	500 g
	Hydroxypropyl methyl cellulose phthalate	57 g
III	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The pellets were prepared as described in Example 2 above.

Properties of the enteric coated pellets

For the preparations according to Examples 2 - 8 and comparative Examples I - V above one or both of the following studies have been performed.

Acid resistance

The acid resistance of the formulations was studied in the following way: The formulations were added to gastric fluid USP (without enzyme), 37°C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulations was determined.

Rate of dissolution in buffer solution

In order to establish the rate of dissolution in the small intestine, the formulations were added to a buffer solution. Buffer solution 37°C, USP dissolution apparatus No 2 (paddle), 100 r/min. After 10 or 30 minutes the amount of omeprazole dissolved was determined. The results are presented in the following Table 5.

Table 5

Example No	*Omeprazole content mg/g*	*Acid resistance, amount intact omeprazole (%) after 2 hours*	*% dissolved omeprazole at different pH:s and after 10 or 30 min*		
			%	*pH*	*min*
2	89.2	95	100	6.8	10
3	90	96	91	6.0	10
4	88	89	*)		
5	82	93	70	7.5	30
6	81.3	87	93	6.8	10
7	91	95	**)		
8	89	98	**)		
I	93	97	*)		
II	92	94	*)		
III	94	58	*)		
IV	86.5	4			
V	91	93	**)		

*) The stability of the formulations was studied during storage in glass bottles also containing a desiccant device. After one month storage at +50°C the formulation according to Example 4 was virtually intact with no change in appearance or physicochemical characteristics. Pellets according to Examples I and II turned brown due to degradation, while the pellets according to Example III retained the original white colour.

**) The formulations according to Examples 7 and 8 were white and not affected by the coating process. The enteric coated pellets according to Example V, where the enteric coating was applied directly on the cores according to Example 8, was discoloured already during the enteric coating process.

Further comparative test

This example demonstrates the effect of the moisture content of the preparations according to the invention on storage stability.

The stability of omeprazole pellets according to the invention was compared with that of omeprazole pellets with higher water content. Omeprazole pellets were prepared according to the invention with a water content of 1 %. Two other portions of the same formulation were conditioned to a water content of 2 % and 5 % respectively. The three formulations, packed in tight containers not containing a desiccant, were stored for one month at +50°C. After this time the packages were opened and the pellets were assayed for the amount of omeprazole by HPLC. The formulation according to the invention had an omeprazole content of 98.5% of the initial value. The other two formulations with a water content of 2 and 5 % respectively were virtually totally degraded and had only trace amounts of intact omeprazole.

Discussion

From the results given in Table 5 it can be seen that formulations containing omeprazole with acceptable acid resistance can be prepared by using a conventional enteric coating technique (see for instance Examples I, II and V). However, it is also obvious that the storage stability of the formulations according to Examples I, II and V is not acceptable, since a discolouration, showing a degradation of omeprazole, occurs during short storage at an elevated storage temperature (Examples I and II) or already during the enteric coating process (Example V).

If the amount of alkaline substances in the cores is increased to a level where omeprazole has an acceptable storage stability (Example III) or if an alkaline reacting salt of omeprazole is used in the preparation of the cores (Example IV), then, without the separating layer of the invention, the resistance to dissolution in acid media becomes unacceptably low and much or all of the active substance will degrade already in the stomach and thus, it has no effect on the gastric acid secretion.

When the preparation is carried out according to the invention as for instance in Example 4, a good resistance towards gastric juice as well as a good stability during long-term storage is obtained. This is in contrast with the formulations in Examples I, II and III where either an acceptable acid resistance or an acceptable storage stability can be achieved - but not both. The same comparison can be made between the formulations according to Examples 7 and 8 according to the invention and the formulation according to Example V, where the separating layer was omitted. Examples 7 and 8 differ in that a buffering substance, magnesium hydroxide, has been included in the cores of Example 8. This further improves the acid resistance as well as the storage stability of Example 8 in comparison with Example 7.

The further comparative test shows the great importance of a low water content in the preparations.

Thus in order to prepare pharmaceutical formulations of omeprazole for oral use, which expert good stability during long-term storage as well as good stability during the residence in the stomach after administration, the preparation is made in the following way:

a) Omeprazole together with an alkaline reacting compound or compounds or an alkaline reacting salt of omeprazole optionally mixed with alkaline reacting compound are included in the core material.

b) The core material is subcoated with one or more inert, in water soluble or in water rapidly disintegrating layers, which separate the alkaline reacting core from the enteric coating. The subcoating layer may optionally contain pH-buffering compounds.

c) The subcoated cores are coated with an acid insoluble enteric coating, optionally containing plasticizers.

Biopharmaceutical studies

The hard gelatin capsules according to Example 2 were administered to 12 healthy, young male volunteers in the following way:

The volunteers came to the laboratory in the morning after having abstained from food since 10 p.m. the night preceeding the experimental day. A zero time blood sample was taken. One omeprazole capsule according to Example 2 was administered together with 150 ml of tap water. Further blood samples were taken during the day.

In another experiment the same volunteers were administered 20 mg of omeprazole in the form of a suspension of micronized omeprazole in a sodium bicarbonate water solution. In order to reduce the degradation of omeprazole in the stomach to a minimum, sodium bicarbonate solution were given to the subjects just before the administration of the omeprazole suspension and at further four times with a 10-minutes interval after the drug intake. The concentration of omeprazole in blood plasma was assayed by high pressure liquid chromatography (Persson, Lagerström and Grundevik. Scand J Gastroenterol 1985, *20*, (suppl 108), 71-77. The mean plasma concentrations are given in Table 6.

Table 6

Mean plasma concentrations (μmol/l) after 20 mg single oral doses of omeprazole given as hard gelatin capsules according to Example 2 and as a suspension of micronized omeprazole in sodium bicarbonate solution.

Time (min)	*Capsules*	*Suspension*
10		0.84
20		0.90
30	0.03	0.84
45		0.64
60	0.22	0.44
90	0.36	0.24
120	0.39	0.13
150	0.29	
180	0.20	0.04
210	0.10	
240	0.05	0.01
300	0.02	0
360	0.01	
420	0	

Although the plasma concentrations peak at different times, the two formulations are bioequivalent. The mean relative bioavailability of the capsules in comparison with the suspension was 85% ±23% (S.D.). The comparison was based on the total area under the individual plasma concentration versus time curves.

Thus, by preparing capsules according to the invention it is possible to obtain a preparation with the same bioavailability as a suspension containing the same amount of micronized active compound. It is, however, to be noticed that when the suspension is administered, the patients must also be given sodium bicarbonate solution frequently in order to minimize pre-absorption degradation of omeprazole in the stomach.

CLAIMS

1. An oral, pharmaceutical preparation containing omeprazole as the active ingredient characterized in that it is composed of core material containing omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, film forming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n is not an integer and less than 2.

3. A preparation according to claim 1 wherein the subcoating comprises two or more sub-layers.

4. A preparation according to claim 3 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

5. A preparation according to any one of the preceding claims wherein the alkaline core comprises omeprazole and an inert pH-buffering alkaline compound rendering the micro-environment of omeprazole a pH of 7-12.

6. A preparation according to claim 5 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds [Al_2O_3.6MgO.CO_2.12H_2O or MgO.Al_2O_3.2SiO_2.nH_2O], wherein n is not an integer and less than 2.

7. A preparation according to any one of claims 1-4 wherein the alkaline core comprises an alkaline salt of omeprazole such as the sodium, potassium, magnesium, calcium or ammonium salt.

8. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of omeprazole mixed with an inert, alkaline compound.

9. A preparation according to any one of the preceding claims wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, copolymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

10. A preparation according to any one of the preceding claims wherein the water content of the final dosage form containing omeprazole is not more than 1.5% by weight.

11. Process for the preparation of an oral pharmaceutical formulation containing omeprazole in which cores containing omeprazole mixed with an alkaline reacting compound or compounds or an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound or compounds are coated with one or more subcoating layers whereafter the subcoated cores are further coated with an enteric coating.

12. Process according to claim 11 wherein a preparation according to any one of claims 2-10 is prepared.

13. A method for the treatment of gastrointestinal disease characterized in that a preparation according to any one of claims 1-10 is administered to a host in the need of such treatment in the therapeutically effective amount.

14. Use of a preparation according to any one of claims 1-10 for the manufacture of a medicament for treatment of gastrointestinal diseases.

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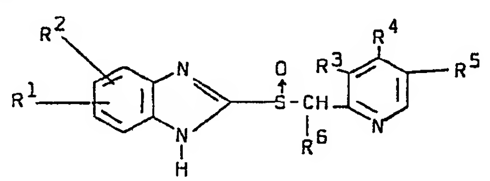
(54) **Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.**

(57) The present invention relates to novel compounds of the formula



wherein R^1 and R^2 are same or different and are each hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, or alkanoyl, R^6 is hydrogen, methyl or ethyl, R^3, R^4 and R^5 are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy whereby R^3, R^4 and R^5 are not all hydrogen, and whereby when two of R^3, R^4 and R^5 are hydrogen the third of R^3, R^4 and R^5 is not methyl. The compounds are potent gastric acid secretion inhibitors.

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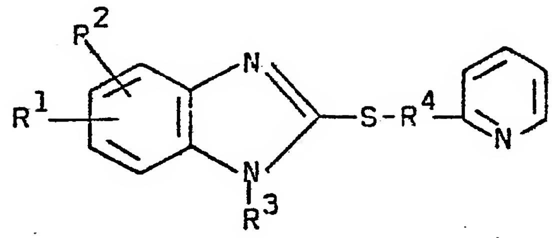
Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

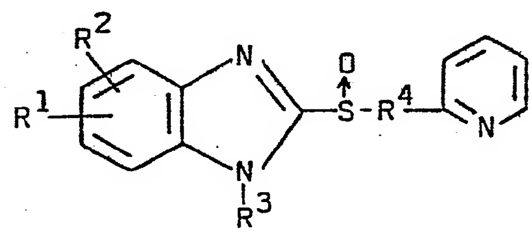
The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man, as well as the process for their preparation, method of affecting gastric acid secretion and pharmaceutical preparations containing said novel compounds.

The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

It is previously known that compounds of the formulas I and II



(I)

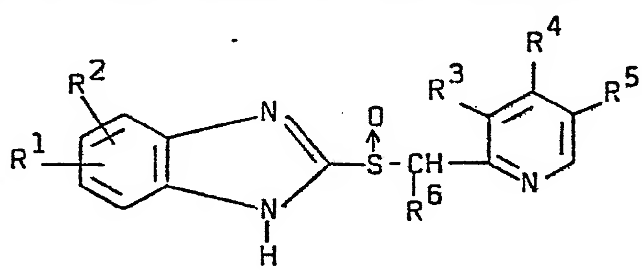


(II)

wherein R^1 and R^2 are each selected from the group consisting of hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoyloxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl and acyl in any position, R^3 is selected from the group consisting of hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, and alkylsulphonyl, and R^4 is selected from the group consisting of straight and branched alkylene groups having 1 to 4 carbon atoms, whereby at most one methylene group is present between S and the pyridyl group, and whereby the pyridyl group may be further substituted with alkyl or halogen, possess inhibiting effect of gastric acid secretion.

It has now, however, surprisingly been found that the compounds defined below possess a still greater inhibiting effect than those given above.

Compounds of the invention are those of the general formula III



(III)

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4 and R^5 are same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4 and R^5 is not methyl.

Alkyl R^1 and R^2 of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

Halogen R^1 and R^2 is chloro, bromo, fluoro, or iodo.

Alkoxy R^1 and R^2 are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

Alkanoyl R^1 and R^2 have preferably up to 4 carbon atoms and are e.g. formyl, acetyl, or propionyl, preferably acetyl.

A preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen the third of R^3, R^4, and R^5 is not methyl.

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A second preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3 is methyl, R^4 is methoxy, and R^5 is methyl.

A third preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 is hydrogen, R^4 is methoxy and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen.

A fourth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is methoxy.

A fifth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are methyl and R^4 is hydrogen.

A sixth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy.

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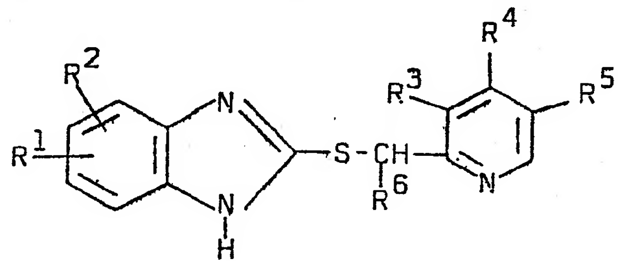
A seventh preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3, R^4, and R^5 are all methyl.

Compounds of formula III above may be prepared according to the following methods:

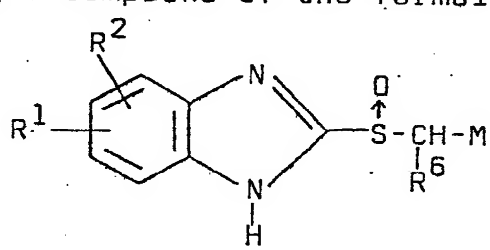
a) oxidizing a compound of formula IV



(IV)

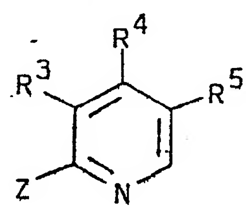
wherein R^1, R^2, R^6, R^3, R^4, and R^5 have the meanings given, to the formation of a compound of formula III.

b) reacting a compound of the formula V



(V)

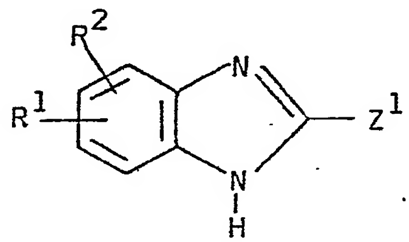
wherein R^1, R^2, and R^6 have the meanings given above and M is a metal selected from the group consisting of K, Na and Li, with a compound of formula VI.



(VII)

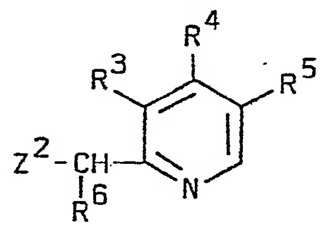
wherein R^3, R^4, and R^5 have the same meanings as given above, Z is a reactive esterified hydroxy group, to the formation of a compound of formula III;

c) reacting a compound of the formula VII



(VII)

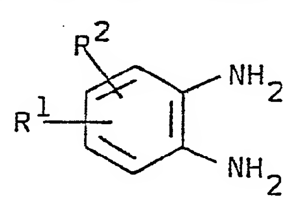
wherein R^1, and R^2 have the same meanings as given above and Z^1 is SH or a reactive esterified hydroxy group, with a compound of the formula VIII



(VIII)

wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, and Z^2 is a reactive esterified hydroxy group or SH, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III;

d) reacting a compound of the formula IX



(IX)

wherein R^1 and R^2 have the same meanings as given above with a compound of the formula X

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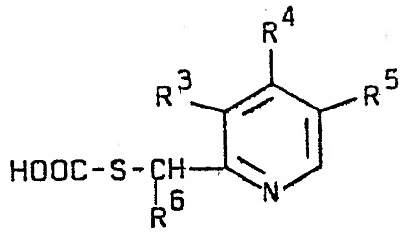


(X)

wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z^1, and Z^2 may be a reactive, esterified hydroxy group which is a hydroxy group esterified with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent selected from the group consisting of nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui

or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may form salts with organic or inorganic aoids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.

Some of the new compounds may, depending on the choice of starting materials and process, be present as optical isomers or racemate, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystal-

lization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid, Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known _per se_.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95 % by weight of the preparation, between 0.5 to 20 % by weight in preparations for injection and between 2 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an anti-friction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed

into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2 % to 20 % by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 % to 10 % by weight. These solutions may also contain stabilizing agents and/or

buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20.000 to 200.000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates a preferred embodiment of the invention without being limited thereto. Temperature is given in degrees Centigrade.

The starting materials in the examples found below were prepared in accordance with the following methods:
(1) a 1,2-diamino compound, such as o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptobenzimidazole;
(2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448-451 (1956));
(3) the compound 2-chloromethylbenzimidazole was prepared by condensing o-phenylenediamine with chloroacetic acid.

Example 1

28.9 g of 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)-benzimidazole were dissolved in 160 ml of $CHCl_3$, 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with CH_2Cl_2, washed with Na_2CO_3 solution, dried over Na_2SO_4 and evaporated *in vacuo*. The residue crystallized when diluted with CH_3CN, and 2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole was recrystallized from CH_3CN. Yield 22.3 g; m.p. 158°C.

Examples 2-30

The preparation of compounds of formula III labelled 2-26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table 1 which identifies the substituents for these compounds.

Example 31 (method c)

0.1 moles of 4-6-dimethyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated *in vacuo*. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl)pyridylmethylthio]-(4,6-dimethyl)benzimidazole was isolated. Yield 0.05 moles.

This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound, melting point 50-55^{o}C.

Example 32 (method b)

0.1 moles of 2-[Li-methylsulfinyl](5-acetyl-6-methyl)-benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was filtered off, and the solution was evaporated *in vacuo*. The residue was crystallized from CH_3CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole melting at 171^{o}C.

Example 33 (method d)

23.4 g of 2-[2-(3,4,5-trimethyl)pyridylmethylthio] formic acid and 16.6 g of o-(5-acetyl-6-methyl)phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was

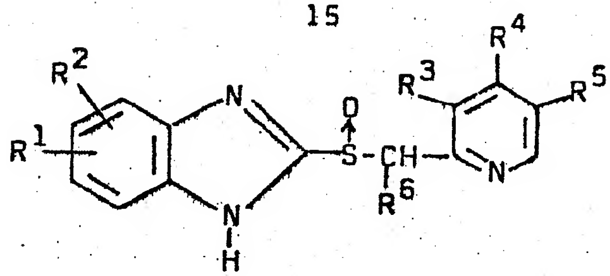
treated with active carbon and evaporated <u>in vacuo</u>. The residue was dissolved in acetone whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-(5-acetyl-6-methyl)benzimidazole was 6.5 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 190°C.

Example 34 (method c)

22.0 g of 2-mercapto-(5-acetyl-6-methyl)benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95 % ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated <u>in vacuo</u>. The residue, 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole, was recrystallized from 70 % ethanol. Yield 10.6 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 158°C.



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	M.p. °C
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	158
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	163
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	141
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	160
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	163
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	50-55
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	171
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	190
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	165
10	4-CH_3	6-CH_3	H	H	OCH_3	H	122
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	156
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	144
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	185
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	169
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	148
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	175
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	155
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3	158
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	141
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	142
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	162
22	5-OCH_3	H	H	H	OCH_3	CH_3	178
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	156
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	181
25	H	H	H	CH_3	OCH_3	CH_3	165
26	5-Cl	H	H	CH_3	OCH_3	CH_3	185
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	119
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	150-5
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	130
30	5-CH_3	H	CH_3	CH_3	H	CH_3	152

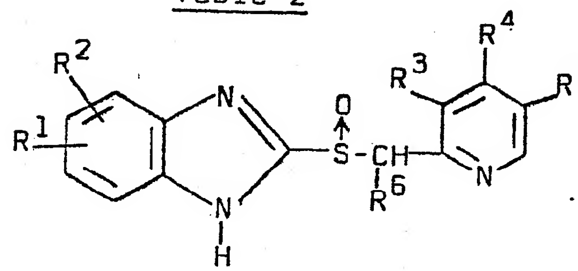
Biological effect

The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed on conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administration of the test compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1-4 nmol/kg, h) lasting for 6-7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol H^+/60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, suspended in 0.5 % Methocel® (methyl cellulose), were given intraduodenally in doses from 4-20 µmol/kg when the secretory response to pentagastrin has reached a steady level.

In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.

The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Table 2



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	2	90
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	1	60
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	2	100
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	100
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	2	95
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	70
x	5-$COCH_3$	6-CH_3	H	H	CH_3	H	20	30
x	5-$COCH_3$	6-CH_3	H	H	H	CH_3	8	80
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	2	60
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	2	90
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	2	70
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	80
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	2	100
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	4	75
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	0.5	65
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	90
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3		
x	5-$COOCH_3$	6-CH_3	H	H	H	CH_3	4	50
x	5-$COOCH_3$	6-CH_3	H	Br	H	H	4	0
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	4	40
10	4-CH_3	6-CH_3	H	H	OCH_3	H	2	40
x	4-CH_3	6-CH_3	H	H	H	H	4	30
x	4-CH_3	6-CH_3	H	H	H	CH_3	12	50

cont.

Ex	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	4	100
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	2	60
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-$COOCH_3$	H	H	H	H	CH_3	20	90
x	5-$COOCH_3$	H	H	H	H	H	20	50
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	60
x	5-$COCH_3$	H	H	H	H	C_2H_5	20	40
22	5-OCH_3	H	H	H	OCH_3	CH_3		
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-OCH_3	H	H	H	CH_3	H	20	10
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	0.5	50
x	5-CH_3	H	H	H	H	CH_3	4	50
25	H	H	H	CH_3	OCH_3	CH_3	0.5	60
x	H	H	H	H	H	H	4	50
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	0.5	50
26	5-Cl	H	H	CH_3	OCH_3	CH_3	0.5	25
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	0.5	30
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	0.5	40

x denotes a previously known compound

Example 35

A syrup containing 2 % (weight per volume) of active substance was prepared from the following ingredients:

2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]--(5-acetyl-6-methyl)benzimidazole · HCl	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavouring agent	0.1 g
Ethanol 96 %	10.0 ml
Distilled water (sufficient to obtain a final volume of 100 ml)	

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 36

2-[2-(3,4-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10 % solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

Granules were prepared from 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a 10 % alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %), and dyestuff (0.2 %). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66 % sugar syrup and polished with a solution of 10 % carnauba wax in carbon tetrachloride.

Example 38

2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole hydrochloride (1 g), sodium chloride (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Claims

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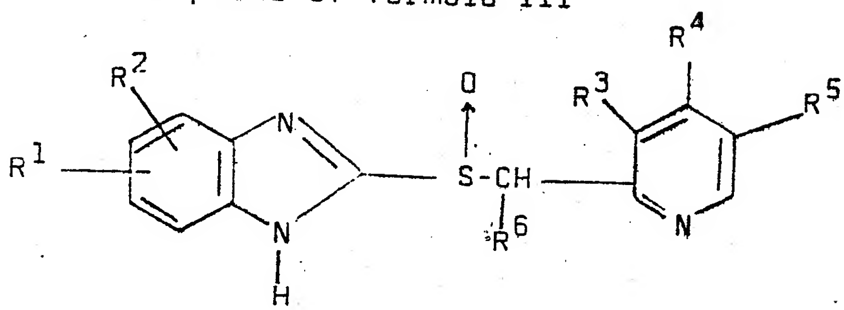
1. A compound of formula III



(III)

or a therapeutically acceptable salt thereof in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

2. A compound according to claim 1, wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl in any position, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 are not methyl.

3. A compound according to claim 1,wherein R^1, R^2, and R^6 have the meanings given and R^3 and R^5 are methyl and R^4 is methoxy.

4. A compound according to claim 1, wherein R^1, R^2, and R^6 have the meanings given, R^4 is methoxy, and R^3 is hydrogen and R^5 is methyl, or R^5 is hydrogen and R^3 is methyl.

5. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2, and R^6 have the meanings given, R^3 and R^5 are hydrogen, and R^4 is methoxy, ethoxy, methoxyethoxy or ethoxy-ethoxy.

6. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2,and R^6 have the meanings given, and R^3, and R^5 are methyl and R^4 is hydrogen.

7. A compound according to claim 1 and selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimetnyl)-benzimidazole

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

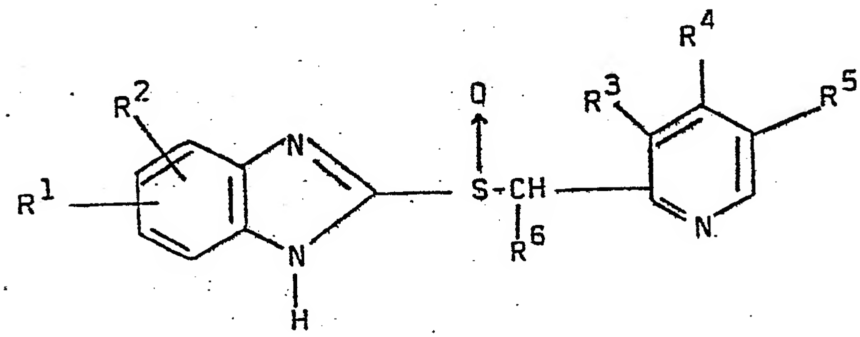
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole

8. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound of formula III



(III)

or a pharmaceutically acceptable non-toxic acid addition salt thereof in a therapeutically effective amount in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

9. A pharmaceutical preparation according to claim 8 wherein the active ingredient is selected from the group consisting of

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2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

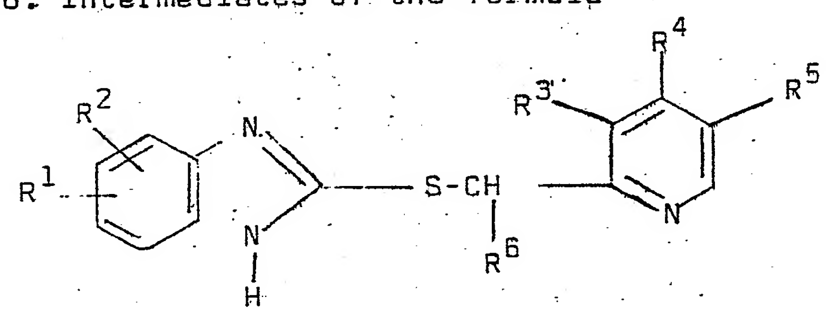
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole,

or a pharmaceutically acceptable non-toxic addition salt thereof.

10. Intermediates of the formula



wherein R^1 and R^2, preferably in 3 to 5 position, are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4, and R^5 are the same or different and are selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5

are not all hydrogen when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

0005129

Application number

European Patent Office

EUROPEAN SEARCH REPORT

EP 79 85 0022

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	DE - A - 2 548 340 (AB HÄSSLE) * pages 1 to 12 * ------	1,24

CLASSIFICATION OF THE APPLICATION (Int. Cl.²)

C 07 D 403/12
A 61 K 31/44

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

C 07 D 403/12
A 61 K 31/44

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18-07-1979	DE BUYSER

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The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

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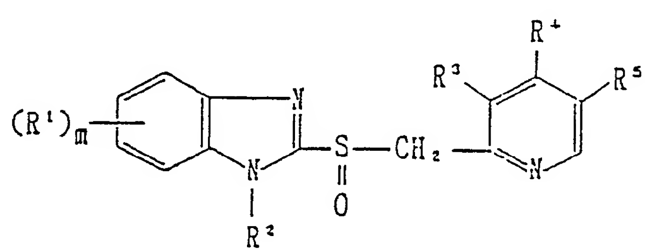
(54) **Stabilized pharmaceutical composition comprising a benzimidazole compound, its production and its use as an antiulcer agent.**

(57) The pharmaceutical composition of the invention, which comprises a benzimidazole compound of the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, is physically stable.

EP 0 237 200 A2

Stabilized Pharmaceutical Composition and Its Production

This invention relates to a pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulphinyl]-benzimidazole or a derivative thereof (hereinafter sometimes referred to collectively as "benzimidazole compounds"), which is useful as an antiulcer agent, as stabilized by incorporation of a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium and its production.

Certain benzimidazole compounds have recently been under clinical study as gastric acid secretion inhibitors. They serve as therapeutic agents for digestive ulcers. Their principal pharmacological effect consists in gastric acid secretion suppression based on $(H^+ + K^+)$-ATPase inhibition and is more potent and durable as compared with histamine H_2 receptor antagonists such as cimetidine and ranitidine. They also have gastric mucosa protecting activity. Therefore, they have attracted attention as next-generation potent therapeutic agents for digestive ulcers.

Those benzimidazole compounds which are described in Japanese Unexamined Patent laid open Nos. 62275/77, 141783/79, 53406/82, 135881/83, 192880/83 and 181277/84, corresponding to U.S. Patent No. 4,045,563, U.S. Patent No. 4,255,431, European Patent Publication No. 45,200, U.S. Patent No. No. 4,472,409, European Patent Publication No. 5,129 and G.B. Patent Publication No. 2,134,523A, respectively, among others are known to have antiulcer activity.

These compounds, however, have poor stability. In the solid state, they are susceptible to heat, moisture and light and, in aqueous solution or suspension, their stability decreases with decreasing pH. In dosage forms, i.e. tablets, powders, fine granules, granules and capsules, said compounds are apt to interact with other components contained in said dosage forms and accordingly are in a less stable state as compared with the case where they occur alone. Thus, the content decreases and the color changes significantly in the manufacturing process of dosage form and with the lapse of time. Microcrystalline cellulose, polyvinylpyrrolidone (PVP), carboxymethylcellulose calcium, polyethylene glycol 6000 and Pluronic F68 (polyoxyethylene-polyoxypropylene copolymer), for instance are dosage form components adversely affecting the stability of said compounds. Furthermore, in the case of coated tablets and coated granules among the above dosage forms, enteric coating bases such as cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate and Eudragit (methacrylic acid-acrylic acid copolymer) have poor compatibility with said compounds and cause content decrease and color change. Nevertheless, one or more of these components or ingredients, which, as mentioned above, can produce adverse effects on the stability of said compounds, are essential in the manufacture of oral preparations and therefore difficulties are inevitably encountered in dosage form manufacture.

The prior art avoids the above-mentioned stability problem by using said benzimidazole compounds in a salt form, say in the form of a lithium, sodium, potassium, magnesium, calcium or titanium salt [Japanese Unexamined Patent laid open No. 167587/84 (European Patent Publication No. 124,495A)]

However, the above prior art method requires, for the stabilization of the benzimidazole compounds, a step of converting said compounds to such a salt form as mentioned above in advance.

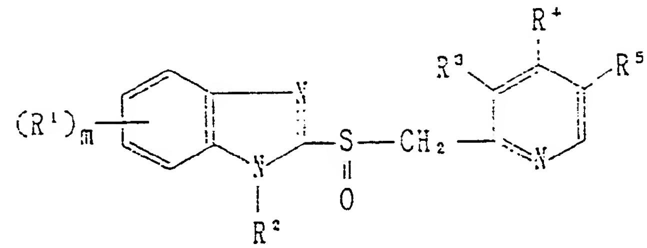
In view of the above, the present inventors made in vestigations in an attempt to stabilize pharmaceutical preparations containing benzimidazole compounds and, as a result, have completed the present invention.

Thus, this invention relates to

(1) A pharmaceutical composition which comprises 2-[(2-pyridyl)methylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and

(2) A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition containing 2-[(2-pyridylmethylsulfinyl]benzimidazole or a derivative thereof, which has an antiulcer activity.

The benzimidazole compounds having an antiulcer activity which are to be used in the practice of the invention are those compounds which are described in the above-cited laid-open patent specifications, for instance and are represented by the formula



(I)

wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

The compounds of the formula(I) can be produced by the methods described in the above-cited laid-open patent specifications or modifications thereof.

In the following, brief mention is made of the substituents in those compounds which have the formula - (I) and are already known.

Referring to R^1 in the above formula, C_{1-7} alkyls may be mentioned as the alkyl represented by R^1; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxyalkyl and C_{1-4} alkyls as the alkyl moiety; C_{1-4} alkyls as the alkyl moiety of the carbamoylalkyl; C_{1-5} alkoxys as the alkoxy; C_{1-7} alkyls as the alkyl moiety of the hydroxyalkyl; C_{1-4} alkanoyls as the acyl; phenyl as the aryl; phenyl as the aryl moiety of the aryloxy; C_{1-6} alkyls as the alkyl moiety of the alkylthio; and C_{1-6} alkyls as the alkyl moiety of the alkylsulfinyl.

Referring to R^2, C_{1-5} alkyls may be mentioned as the alkyl represented by R^2; C_{1-4} alkanoyls as the acyl; C_{1-4} alkoxys as the alkoxy moiety of the carboalkoxy; C_{1-4} alkyls as the alkyl moiety of the alkylcarbamoyl; C_{1-4} alkyls as each of the alkyl moieties of the dialkylcarbamoyl; C_{1-4} alkyls as the alkyl moiety of the alkylcarbonylmethyl; C_{1-4} alkoxys as the alkoxy moiety of the alkoxycarbonylmethyl; and C_{1-4} alkyls as the alkyl moiety of the alkylsulfonyl.

Referrring to R^3, R^4 and R^5, C_{1-4} alkyls may be mentioned as the alkyl represented by any of them; C_{1-8} alkoxys as the alkoxy; and C_{1-4} alkoxys as each of the alkoxy moieties of the alkoxyalkoxy.

Referring to R^4, C_{1-8} alkoxys may be mentioned as the alkoxy, which may optionally be fluorinated.

Among those compounds of the above formula (I), (I) the compounds of which R^1 is hydrogen, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 and R^5 are the same or different and each is hydrogen or methyl, R^4 is fluorinated C_{2-5} alkoxy and m is I, (2) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is hydrogen or methyl, R^4 is C_{3-8} alkoxy, R^5 is hydrogen and m is I, and - (3) the compounds of which R^1 is hydrogen, fluorine, methoxy or trifluoromethyl, R^2 is hydrogen, R^3 is C_{1-8} alkoxy, R^4 is C_{1-8} alkoxy which may be fluorinated, R^5 is hydrogen and m is I.

Detailed mention is now made of the substituents in such novel compounds.

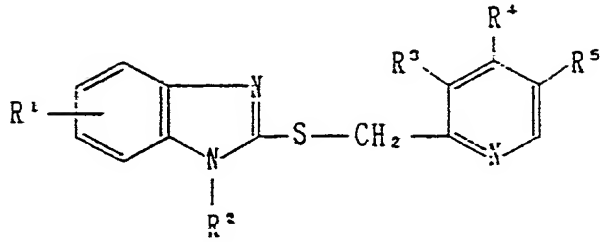
Referring to R^3, the lower alkyl represented thereby is preferably C_{1-8} lower alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy and more preferably C_{1-4} lower alkoxy.

Referring to R^4, C_{1-8} lower alkoxys may be mentioned as the lower alkoxy, which may optionally be fluorinated, and preferred examples are as mentioned above for R^3. As the fluorinated lower alkoxy, there may be mentioned, for example, 2,2,2-trifluoroethoxy, 2,2,3,3,3-pentafluoropropoxy, 1-(trifluoromethyl)-2,2,2-trifluoroethoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,4,4,4-heptafluorobutoxy and 2,2,3,3,4,4,5,5-octafluoropentoxy, and fluorinated C_{2-4} lower alkoxys are preferred.

The position of R^1 is position 4 or position 5, preferably position 5.

Some methods of producing the above novel compounds [hereinafter referred to as "compounds of formula (I')"] are described below.

Said compounds can be produced by subjecting a compound of the formula



(II)

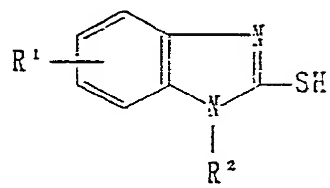
wherein R^1-R^5 are as defined above, to oxidation.

The oxidizing agent to be used is, for example, meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, permaleic acid or the like peracid, sodium bromite or sodium hypochlorite. Examples of the solvent to be used in carrying out the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, and water. These solvents may be used either singly or in admixture. Said oxidizing agent is used preferably in an amount approximately equivalent or slightly excessive relative to the compound (II). Thus, said agent is used in an amount of about 1-3 equivalents, more preferably about 1 to 1.5 equivalents. The reaction is carried out at a temperature from about 0°C (ice cooling) to around the boiling point of the solvent used, generally at a temperature from about 0°C (ice cooling) to room temperature, preferably at a temperature of about 0°C to 10°C. The reaction time is generally about 0.1 to 24 hours, preferably about 0.1 to 4 hours.

The desired novel compounds (I') produced by the above reaction can be isolated and purified by conventional means such as recrystallization, chromatography and so on.

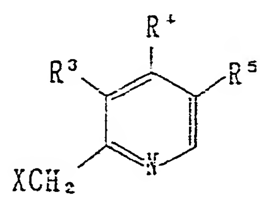
Said compounds may be converted to pharmacologically acceptable salts by conventional means. As such salts, there may be mentioned hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate, among others.

The novel compounds (II) can be produced by reacting a starting compound of the formula



(III)

wherein R^1 and R^2 are as defined above, with a starting compound of the formula



(IV)

wherein R^3-R^5 are as defined above and X is a halogen atom.

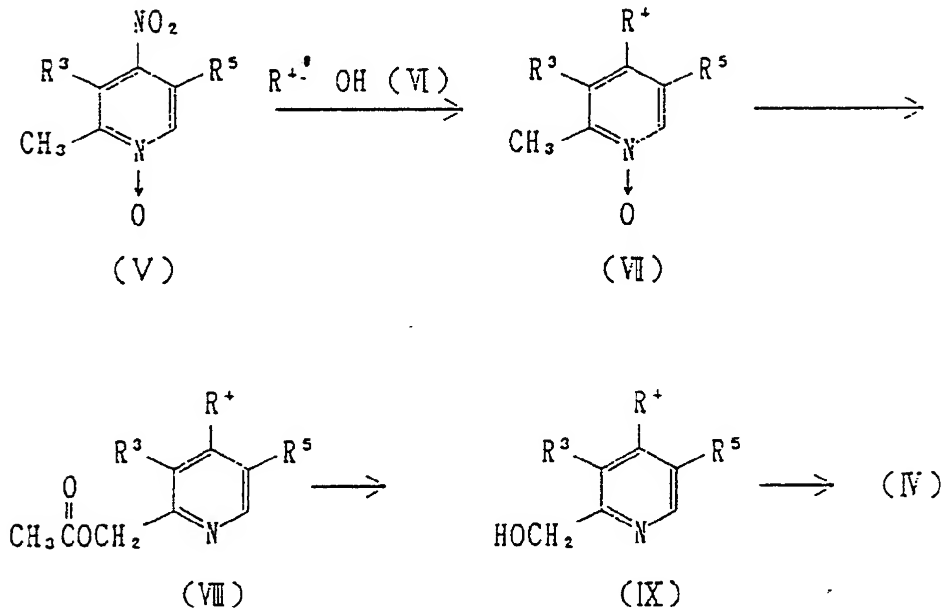
The halogen atom represented by X is, for example, chlorine, bromine or iodine.

The reaction is carried out advantageously in the presence of a base. As said base, there may be mentioned alkali metal hydrides such as sodium hydride and potassium hydride, alkali metals such as metallic sodium, sodium alcoholates such as sodium methoxide and sodium ethoxide, alkali metal carbonates such as potassium carbonate and sodium carbonate, and organic amines such as triethylamine, among others. As the solvent to be used in carrying out the reaction, there may be mentioned, for example, alcohols such as methanol and ethanol, and dimethylformamide. The base is used generally in an amount slightly excessive relative to the equivalent amount but may also be used in a large excess. Thus, it is used in an amount of about 2-10 equivalents, preferably about 2-4 equivalents. The above reaction is carried out generally at a temperature of about 0°C to around the boiling point of the solvent used, preferably at about 20°C to 80°C, for a period of about 0.2-24 hours, preferably about 0.5-2 hours.

Some methods of producing the starting compounds (IV) are described below.

Among the compounds (IV), those compounds wherein R^3 and R^5 are the same or different and each is hydrogen or methyl and R^4 is fluorinated C_{2-5} alkoxy or C_{3-8} alkoxy can be produced by the following process:

Process 1)



A nitro compound of the formula (V), wherein R^3 and R^5 are as defined above, is reacted with an alcohol derivative of the formula $R^{4'}OH$ (VI) wherein $R^{4'}$ is fluorinated C_{2-5} alkyl or C_{3-8} alkyl, in the presence of a base to give an alkoxy derivative of the formula (VII) wherein R^3, R^4 and R^5 are as defined above. The base to be used in carrying out the reaction includes, among others, alkali metals such as lithium, sodium and potassium, alkali metal hydrides such as sodium hydride and potassium hydride, alcoholates such as potassium t-butoxide and sodium propoxide, alkali metal carbonates and hydrogen carbonates such as potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate,
and alkali metal hydroxides such as
sodium hydroxide and potassium hydroxide. The alcohol derivative to be submitted to the reaction includes, among others, propanol, isopropanol, butanol, pentanol, hexanol, 2,2,2-trifluoroethanol, 2,2,3,3,3-pentafluoropropanol, 2,2,3,3-tetrafluoropropanol, 1-(trifluoromethyl)-2,2,2-trifluoroethanol, 2,2,3,3,4,4,4-heptafluorobutanol and 2,2,3,3,4,4,5,5-octafluoropentanol. While $R^{4'}OH$ itself may be used as a solvent in carrying out the reaction, ethers such as tetrahydrofuran and dioxane, ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide, for instance, may also be used as solvents. An appropriate reaction tem perature may be selected within the range of about 0°C (ice cooling) to around the boiling point of the solvent used. The reaction time is about 1-48 hours.

Heating (about 80-120°C) of the thus-obtained compound (VII) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid gives an 2-acetoxymethylpyridine derivative of the formula (VIII) wherein R^3, R^4 and R^5 are as defined above. The reaction period is generally about 0.1-10 hours.

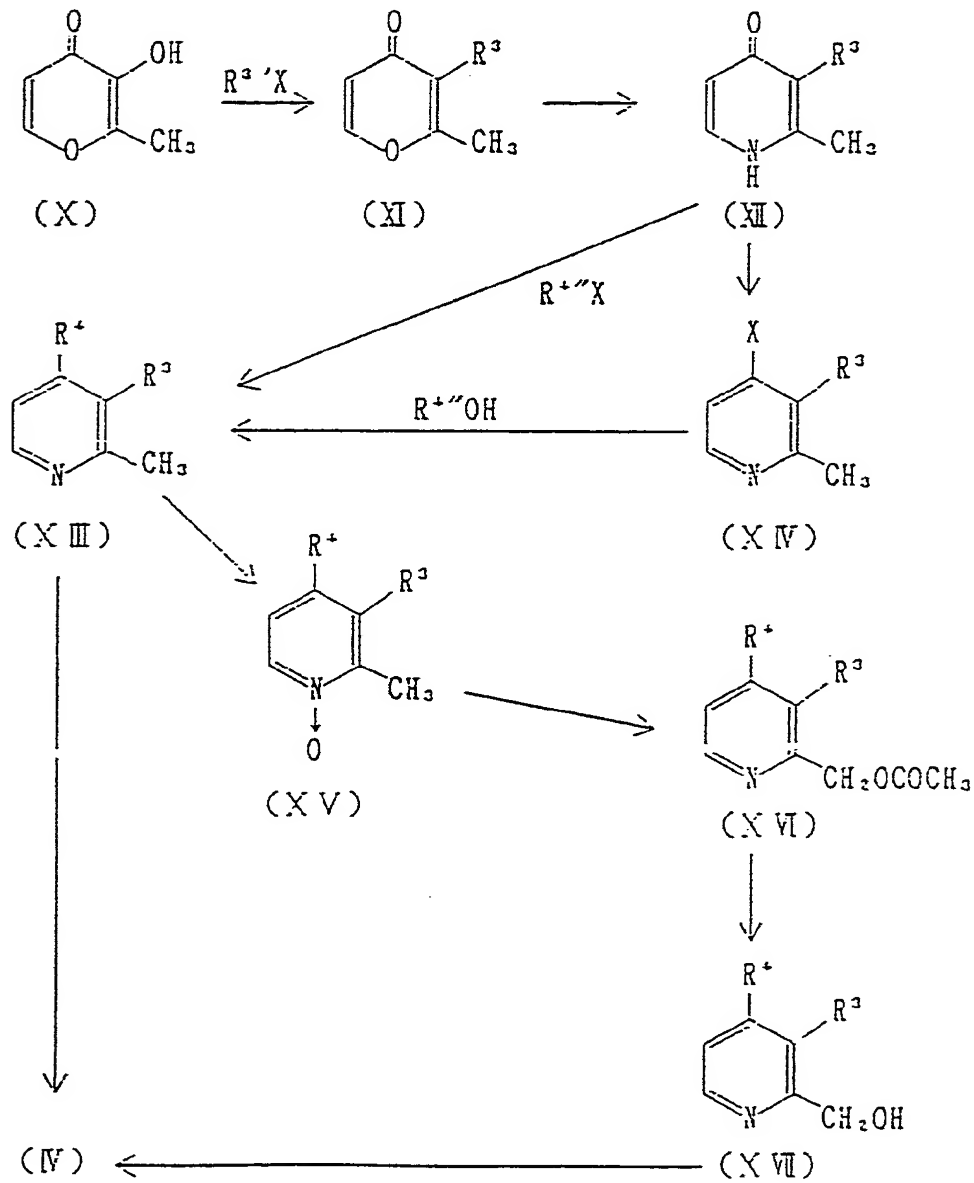
The subsequent alkaline hydrolysis of the compound (VIII) gives a 2-hydroxymethylpyridine derivative of the formula (IX). Sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate, for instance, are usable as alkalis, and methanol, ethanol and water, among others, are usable as solvents. The reaction is generally conducted at about 20-60°C for about 0.1-2 hours.

The compound (IX) is further halogenated with a chlorinating agent such as thionyl chloride to give a 2-halomethylpyridine derivative of the formula (IV) wherein R^3, R^4 and ^{5} are as defined above and X is chlorine, bromine or iodine. Usable as solvents are, for example, chloroform, dichloromethane and tetrachloroethane. The reaction is generally carried out at about 20-80°C for about 0.1-2 hours.

The compound (IV) thus produced occurs in the form of a salt of hydrohalogenic acid corresponding to the halogenating agent used and it is generally preferable to subject said compound to reaction with the compound (III) immediately.

Among the compounds (IV), those compounds wherein R^3 is C_{1-8} lower alkoxy, R^4 is alkoxy which may optionally be fluorinated, and R^5 is hydrogen can be produced by the following process:

Process 2)



Thus, maltol (X) is reacted with a alkyl halide of the formula $R^{3'}X$ in the presence of silver oxide, for instance, to give a compound of the formula (XI). Reaction of (XI) with aqueous ammonia gives a pyridone derivative of the formula (XII). Direct alkylation of the compound (XII) with an alkyl halide, or halogenation of (XII) with a halogenating agent such as phosphorus oxychloride followed by reaction of the resultant halo derivative (XIV) with a lower alcohol of the formula $R^{4''}$ OH in the presence of a base gives a compound of the formula (XIII). The compound (XIII) can be converted to the compound (IV) by direct halogenation with

N-bromosuccinimide or chlorine, for instance. The compound (XIII) may also be converted to the compound (IV) by oxidizing the same with an oxidizing agent such as m-chloroperbenzoic acid, reacting the resulting compound (XV) with acetic anhydride, hydrolyzing the resulting compound (XVI) and halogenating the resulting compound (XVII) with a halogenating agent such as thionyl chloride.

The alkyl halide to be used in the production of the compound (XI) includes, among others, methyl iodide, ethyl iodide, propyl iodide, isopropyl iodide, butyl iodide, pentyl iodide and hexyl iodide, and the alkyl halide to be used in the production of the compound (XIII) further includes, in addition to those mentioned above for use in the production of the compounds (XI), 2,2,2-trifluoroethyl iodide, 2,2,3,3,3-pentafluoropropyl iodide, 2,2,3,3-tetrafluoropropyl iodide, l-(trifluoromethyl)-2,2,2-trifluoroethyl iodide, 2,2,3,3,4,4,4-heptafluorobutyl iodide and 2,2,3,3,4,4,5,5-octafluoropentyl iodide, for instance. Such alkyl iodides are used in an amount of about 1-10 equivalents. Silver oxide, potassium carbonate, sodium carbonate or the like is used as a deacidifying agent and dimethylformamide, dimethylacetamide or the like is used as a solvent. The reaction is generally carried out at room temperature.

The halogenating agent to be used in the production of the compound (XIV) includes, among others, phosphorus oxychloride, phosphorus pentoxide and phosphorus tribromide and is used in an amount of 1 equivalent to a large excess. The reaction is carried out at a temperature of about 50-150°C. The alcohol to be used for the conversion of compound (XIV) to compound (XIII) includes methanol and ethanol and further those alcohol derivatives mentioned for use in process I) and is used in an amount of l equivalent to a large excess, and the base includes those sodium alcoholates and potassium alcoholates which correspond to the respective alcohols as well as potassium t-butoxide, sodium hydride and so forth. An appropriate reaction temperature may be selected within the range of room temperature to the boiling point of the solvent used.

For direct bromination of the compound (XIII) with N-bromosuccinimide, the reaction is preferably carried out under light irradiation, and carbon tetrachloride, chloroform, tetrachloroethane or the like is used as a solvent.

The oxidizing agent to be used for the conversion of compound (XIII) to compound (XV) includes, among others, peracids such as meta-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid as well as hydrogen peroxide. Usable as solvents for the reaction are halogenated hydrocarbons such as chloroform and dichloromethane, ethers such as tetrahydrofuran and dioxane, amides such as dimethylformamide, acetic acid and water, for instance, and these can be used either singly or in admixture. Said oxidizing agent is preferably used in an amount of about l equivalent to an excess relative to the compound (XIII), more preferably about 1-l0 equivalents. The reaction is carried out at a temperature of about 0°C (ice cooling) to around the boiling point of the solvent used generally for a period of about 0.l-24 hours, preferably for about 0.1-4 hours.

The conversion of compound (XV) to compound (XVI) is effected by heating (at about 80-120°C) the compound (XV) with acetic anhydride alone or in the presence of an inorganic acid such as sulfuric acid or perchloric acid and so on. The reaction period is generally 0.1-10 hours.

The alkali to be used in the alkaline hydrolysis of compound (XVI) to compound (XVII) includes, among others, sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. Methanol, ethanol and water, for instance, may be mentioned as usable solvents. The reaction is generally carried out at a temperature of about 20-60°C for a period of about 0.1-2 hours.

For the production of compound (IV) from compound (XVII), a chlorinating agent such as thionyl chloride or an organic sulfonic or organic phosphoric acid chloride such as methanesulfonyl chloride, p-toluenesulfonyl chloride or diphenylphosphoryl chloride is used. When a chlorinating agent such as thionyl chloride is used, it is used in an amount of 1 equivalent to a large excess relative to the compound (XVII) and a solvent such as chloroform, dichloromethane or tetrachloroethane is used, and the reaction is generally carried out at a temperature of about 20-80°C for a period of about 0.1-2 hours. When an organic sulfonic or organic phosphoric acid chloride is used, it is used in an amount of 1 equivalent to a slight excess relative to the compound (XVII) and the reaction is generally carried out in the presence of a base. As usable bases, there may be mentioned organic bases such as triethylamine and tributylamine and inorganic bases such as sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The base is used in an amount of 1 equivalent to a slight excess. As usable solvents, there may be mentioned, for example, chloroform, dichloromethane, carbon tetrachloride and acetonitrile. An appropriate reaction temperature and an appropriate reaction can be selected within the ranges of about 0°C (ice cooling) to around the boiling point and several minutes to several hours, respectively.

The above-mentioned novel benzimidazole compounds have excellent gastric antisecretory activity, gastric mucosa-protecting activity and antiulcer activity but have low toxicity, so that they can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, human).

The basic inorganic salt of magnesium and that of calcium, which are to be used in accordance with the invention, are now described.

Said basic inorganic salt of magnesium includes, among others, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$Mg_6Al_2(OH)_{16}\bullet CO_3\bullet 4H_2O$] and aluminum magnesium hydroxide [$2.5MgO\bullet Al_2O_3\bullet xH_2O$] and said basic inorganic salt of calcium includes, among others, precipitated calcium carbonate and calcium hydroxide. It is only required of such basic inorganic magnesium and calcium salts to show basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension.

Said basic inorganic magnesium and calcium salts may be used either singly or in combination of two or more species in an amount which may vary depending on the kinds thereof but generally lies within the range of about 0.3-20 parts by weight, preferably about 0.6-7 parts by weight, per part by weight of the benzimidazole compounds.

The composition of the invention may further contain such additives as vehicles (e.g. lactose, corn starch, light silicic anhydride, microcrystalline cellulose, sucrose), binders (e.g. α-form starch, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone), disintegrating agents (e.g. carboxymethylcellulose calcium, starch, low substituted hydroxypropylcellulose), surfactants [e.g. Tween 80 (Kao-Atlas), Pluronic F68 (Asahi Denka; polyoxyethylene-polyoxypropylene copolymer], antioxidants (e.g. L-cysteine, sodium sulfite, sodium ascorbate), lubricants (e.g. magnesium stearate, talc), etc.

The composition of the invention is prepared by homogeneously admixing the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

The particle sizes of said benzimidazole compound and said inorganic salt are not especially critical in a condition that they can be homogeneously admixed. For example, preferable particle size is about less than 100 μm, a more preferable one is about less than 20μm.

The moisture amount in the composition is preferably about 6 -60%, more preferably about 20 -40% as equibrium relative humidity (E.R.H).

The method of admixing is optional if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or of calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

Said mixture can be made up into dosage forms suited for oral administration, such as tablets, capsules, powders, granules and fine granules, by per se known means.

Tablets, granules and fine granules may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release property. Usable as coating agents are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, Pluornic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Röhm, West Germany; methacrylic acid-acrylic acid copolymer) and pigments such as titanium oxide and ferric oxide.

Tablets, granules, powders, fine granules and capsules can be produced by a conventional method - (e.g. the method described in the 10th edition of the Japanese Pharmacopeia under General Rules for Preparations). Thus, for example, tablets are produced by adding the basic inorganic salt of magnesium and/or of calcium to a mixture of the benzimidazole compound , vehicle and disintegrant, mixing, adding a binder, granulating the mixture, adding a lubricant etc. and tableting the resultant granular composition. Granules are produced by extrusion in approximately the same manner as in the production of tablets or by coating nonpareils, which contain sucrose and corn starch, with a mixture of benzimidazole compound, a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium, and additives (e.g. sucrose, corn starch, crystalline cellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone)

Capsules are produced by mere mixing and filling. The dosage forms thus obtained show excellent stability with slight changes in appearance and little decreases in content even after storage for a long period of time.

The pharmaceutical composition of the present invention as obtained in the above manner exhibits excellent gastric antisecretory, gastric mucosa-protecting and antiulcer activities and has low toxicity and therefore can be used in the treatment of digestive ulcers in mammals (e.g. mouse, rat, rabbit, dog, cat, pig, human).

The pharmaceutical composition of the invention can be orally administered for the treatment of digestive ulcers in mammals in admixture with pharmacologically acceptable carriers, vehicles, diluents and so forth and in the form of capsules, tablets, granules and some other dosage forms, as mentioned hereinabove. The dose as the benzimidazole compound lies within the range of about 0.01 mg to 30 mg/kg/day, preferably about 0.1 mg to 3 mg/kg/day.

The following reference examples and working examples as well as the experimental examples described later herein illustrate the present invention in more detail but are by no means limitative of the present invention.

Reference Example 1

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethylphosphoric acid triamide (2.07 g) was heated at 70-80°C with stirring for 4.5 days. Then, the insoluble matter was filtered off and the filtrate was concentrated. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract layer was dried over magnesium sulfate, then the solvent was distilled off, and the residue was applied to a silica gel column (50 g). Elution with chloroform-methanol (10:1) and recrystallization from ethyl acetate-hexane gave 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles. Melting point 148-149°C.

The following compounds (VII) were produced from the corresponding compounds (V) in the same manner as above.

Compounds (VII)

	R^3	R^5	R^4	Melting point (°C)
	CH_3	H	OCH_2CF_3	131.0-131.5
Note 1)	H	H	$OCH_2CH_2CH_3$	Oil
Note 2)	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1): NMR spectrum ($CDCl_3$) δ: 1.01 (3H, t, J = 7 Hz), 1.81 (2H, m), 2.50 (3H, s), 3.93 (2H, t, J = 7 Hz), 6.50-6.80 (2H, m), 8.10 (1H, d, J = 7 Hz)

Note 2): NMR spectrum ($CDCl_3$) δ: 1.07 (3H, t J = 7.5 Hz), 1.65-2.02 (2H, m), 2.21 (3H, s), 2.52 (3H, s), 3.99 (2H, t, J = 6 Hz), 6.68 (1H, d, J = 6 Hz), 8.15 (1H, d, J = 6 Hz)

Reference Example 2

Concentrated sulfuric acid (2 drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-l-oxide (2.5 g) in acetic anhydride (8 ml) and the mixture was stirred at 110°C for 2 hours and then concentrated. The residue was dissolved in methanol (30 ml), 2 N aqueous sodium hydroxide (20 ml) was added, and the mixture was stirred at room temperature for 2 hours. After concentration, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, the solvent was then distilled off, and the residue was applied to a silica gel (50 g) column. Elution with chloroform-methanol (10:1) and recrystallization from isopropyl ether gave 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as a brown oil.

NMR spectrum ($CDCl_3$) δ: 2.07 (3H, s), 4.28 (1H, brs), 4.49 (2H, t, J = 12 Hz), 4.67 (2H, s), 6.69 (1H, d, J = 5 Hz), 8.34 (1H, d, J = 5 Hz)

The following compounds (IX) were produced from the corresponding compounds (VII) in the same manner as mentioned above.

Compounds (IX)

	R^3	R^5	R^4	Melting point (°C)
	CH_3	H	OCH_2CF_3	93.5-94.0
Note 1)	H	H	$OCH_2CH_2CH_3$	Oil
Note 2)	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note 1) NMR spectrum ($CDCl_3$) δ: 1.0 (3H, t, J = 7.5 Hz), 1.79 (2H, m), 3.92 (2H, t, J = 6 Hz), 4.51-4.90 (1H, br), 4.68 (2H, s), 6.68 (1H, dd, J = 2 and 6 Hz), 6.80 (1H, d, J = 2 Hz), 8.28 (1H, d, J = 6 Hz)

Note 2) NMR spectrum ($CDCl_3$) δ: 1.03 (3H, t, J = 7.5 Hz), 1.82 (2H, m), 2.02 (3H, s), 3.95 (2H, t, J = 6 Hz), 4.62 (2H, s), 5.20 (1H, brd, s), 6.68 (1H, d, J = 6 Hz), 8.25 (1H, d, J = 6 Hz)

Reference Example 3

Thionyl chloride (0.2 ml) was added to a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) and the mixture was refluxed for 30 minutes and then concentrated. The residue was dissolved in methanol (5 ml) and the solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml). The resultant mixture was refluxed for 30 minutes. The methanol was distilled off, water was added to the residue, and the mixture was extracted with ethyl acetate. The extract was washed with dilute sodium hydroxide solution and dried over magnesium sulfate. The solvent was then distilled off, and the residue was applied to a silica gel (20 g) column. Elution with ethyl acetate-hexane (2:1) and recrystallization from ethyl acetate-hexane gave 370 mg of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl] methylthio]-benzimidazole hemihydrate as colorless plates. Melting point 145-146°C.

The following compounds (II) were produced by reacting the compound (III) with the corresponding compound (IV) in the same manner as mentioned above.

Compounds (II)

	R^1	R^2	R^3	R^5	R^4	Melting point (°C)
	H	H	CH_3	H	OCH_2CF_3	149-150
	H	H	H	H	$OCH_2CH_2CH_3$	84-86
Note)	H	H	CH_3	H	$OCH_2CH_2CH_3$	Oil

Note) NMR spectrum ($CDCl_3$) δ: 0.98 (3H, t, J = 7.5 Hz), 1.54-1.92 (2H, m), 2.15 (3H, s), 3.80 (2H, t, J = 6 Hz), 4.43 (2H, s), 6.55 (1H, d, J = 6 Hz), 7.09 (2H, m), 7.50 (2H, m), 8.21 (1H, d, J = 6 Hz)

Reference Example 4

A solution of m-chloroperbenzoic acid (1.3 g) in chloroform (15 ml) was added dropwise to a solution of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylthio]benzimidazole(2.2 g) in chloroform (20 ml) with ice cooling over 30 minutes and, then, the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated. The concentrate was

applied to a silica gel (50 g) column. Elution with ethyl acetate and recrystallization from acetone-isopropyl ether gave 1.78 g of 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylsulfinyl]benzimidazole [hereinafter sometimes referred to as compound (A)] as pale yellow prisms. Melting point 161-163°C - (decomposition).

The following compounds (I) [hereinafter sometimes referred to as compound (B), compound (C) and compound (D), respectively] were produced in the same manner from the corresponding compounds (II).

Compounds (I)

	R^1	R^2	R^3	R^5	R^4	Melting point (°C)
(B)	H	H	CH_3	H	OCH_2CF_3	178-182 (decomp.)
(C)	H	H	H	H	$OCH_2CH_2CH_3$	123-125 (decomp.)
(D)	H	H	CH_3	H	$OCH_2CH_2CH_3$	81-83

Example I

Of the components given below, the compound (A), magnesium hydroxide, L-cysteine, corn starch and lactose were mixed together, then microcrystalline cellulose, light silicic anhydride and magnesium stearate, each in half the intended amount, were added. After sufficient admixing, the mixture was compression-molded on a dry granulator (roller compactor; Freund, Japan. The compressed mass was ground in a mortar, the resultant granular mass was passed through a round sieve (16 mesh). The remaining portions of microcrystalline cellulose, light silicic anhydride and magnesium stearate were added to the sieved mass and, after admixing, the whole mixture was made up into tablets each weighing 250 mg on a rotary tableting machine (Kikusui Seisakusho, Japan). Composition per tablet:

Compound (A)	50 mg
Magnesium hydroxide	30 mg
L-Cysteine	20 mg
Corn starch	20 mg
Lactose	65.2 mg
Microcrystalline cellulose	60 mg
Light silicic anhydride	1.8 mg
Magnesium stearate	3.0 mg
Total	250.0 mg

Example 2

Tablets were produced in the same manner as in Example I except that omeprazole (Note) was used instead of the compound (A).

Note: 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole

Example 3

Of the components given below, the compound (B), precipitated calcium carbonate, corn starch, lactose and hydroxypropylcellulose were mixed together, water was added, and the mixture was kneaded, then dried in a vacuum at 40°C for 16 hours, ground in a mortar and passed through a 16-mesh sieve to give granules. To this was added magnesium stearate and the resultant mixture was made up into tablets each weighing 200 mg on a rotary tableting machine (Kikusui Seisakusho, Japan). Composition per tablet:

Compound (B)	30 mg
Precipitated calcium carbonate	50 mg
Corn starch	40 mg
Lactose	73.4 mg
Hydroxypropylcellulose	6 mg
Magnesium stearate	0.6 mg
Water	(0.05 ml)
Total	200.0 mg

Example 4

Tablets were produced in the same manner as in Example 3 except that timoprazole (Note) was used instead of the compound (B).

Note: 2-[(2-Pyridyl)methylsulfinyl]benzimidazole

Example 5

The ingredients given below were mixed well in the porportions given below, water was added, and the mixture was kneaded and granulated in an extruder granulator (Kikusui Seisakusho;screen size I.0 mm ϕ). The granules were immediately converted to spherical form in a spheronizer (Fuji Powder's Marumerizer, Japan; 1,000 rpm). The spherical granules were then dried under vacuum at 40°C for I6 hours and passed through round sieves to give I2-to 42-mesh granules. Composition per 200 mg of granules

Compound (B)	30 mg
Heavy magnesium carbonate	20 mg

Corn starch	80 mg
Microcrystalline cellulose	20 mg
Carboxymethylcellulose calcium	10 mg
Hydroxypropylcellulose	10 mg
Pluronic F68	4 mg
Lactose	26 mg
Water	(0.1 ml)
Total	200 mg

Example 6

Granules were produced in the same manner as in Example 5 except that the compound (D) was used instead of the compound (B).

Example 7

Enteric granules were produced by coating the granules obtained in Example 3 with an enteric coating composition specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that the inlet air temperature was 50°C and the granule temperature was 40°C. No. I hard capsules were filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine (Parke-Davis, U.S.A.). Enteric coating composition:

Eudragit L-30D 138 mg (solids 41.4 mg)
Talc 4.1 mg
Polyethylene glycol 6000 12.4 mg
Tween 80 2.1 mg
Water 276µl

Composition of enteric granules:

Granules of Example 5	200 mg
Enteric coat	60 mg
Total	260 mg

Composition per capsule:

Enteric granules	260 mg
No. 1 hard capsule	76 mg
Total	336 mg

Example 8

Of the components given below, the compound (B), magnesium carbonate, sucrose, corn starch and crystalline cellulose were thoroughly mixed together to obtain dusting powder.

Nonpareils were put on a centrifugal fluidized coatinggranulatar (CF-360 Freund, Japan) and then coated with the dusting powder as described above, while spraying hydroxypropylcellulose solution [4% -(w/w)], to give spherical granules. The spherical granules were dried in a vacuum at 40°C for l6 hours and then passed through round sieves to give l2 to 32-mesh granules. Composition per l90 mg of granules:

Nonpareil	75 mg
Compound (B)	15 mg
Magnesium carbonate	15 mg
Sucrose	29 mg
Corn starch	27 mg
Crystalline cellulose	27 mg
Hydroxypropylcellulose [Hydroxypropoxy group content: 53.4-77.5%]	2 mg
Water	(0.05 ml)
Total	190 mg

Example 9

Enteric granules were produced by coating the granules obtained in Example 8 with an enteric coating composition. specified below using a fluidized bed granulator (Okawara, Japan) under conditions such that inlet air temperature was 50°C and the granule temperature was 40°C. No. 2 hard capsules were filled with the enteric granules thus obtained in an amount of 240mg per capsule using a capsule filling machine -(Parke-Davis, USA). Enteric coating composition:

Eudragit L-30D	104.7 mg (solids 31.4 mg)
Talc	9.6 mg
Polyethylene glycol 6000	3.2 mg
Tween 80	1.6 mg
Titanium oxide	4.2 mg
Water	(220 μl)

Composition of enteric granules:

Granules of Example 8	190 mg
Enteric coat	50 mg
Total	240 mg

Composition per capsule:

Enteric granules	240 mg
No. 2 hard capsule	65 mg
Total	305 mg

Experimental Example I

Granules were produced by the method of Example 5 and, after storage at 50°C and 75% RH for I week, were observed for changes in appearance. Granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate or that one of other additives specified below in Table I.

Table 1

Additive	Changes in appearance after 1 week at 50°C and 75% RH
The invention:	
Heavy magnesium carbonate	-
Magnesium oxide	-
Magnesium metasilicate aluminate	-
Synthetic hydrotalcite	-
Aluminum magnesium hydroxide	-
Magnesium silicate	-
Precipitated calcium carbonate	-
Magnesium hydroxide	-
Controls:	
Sodium carbonate	+ (to yellow)
Potassium carbonate	+ (to yellow)
Sodium hydrogen carbonate	+ (to yellow)
Magnesium chloride	++ (to violet)
Magnesium sulfate	++ (to violet)
Calcium chloride	++ (to violet)
Aluminum silicate	+ (to violet)
No additive (lactose)	++ (to violet)

Notes: - : No changes in

+ : Moderately

++ : Severely

As a result, no substantial changes in appearance were noted for the compositions supplemented with the additives of the invention.

Experimental Example 2

Granules were produced in the same manner as in Example 5 except that the compound (A), the compound (C), the compound (D), omeprazole or timoprazole was used instead of the compound (B). After storage at 50°C and 75% RH for I week, they were observed for changes in appearance. As a control to each composition, granules were also produced in the same manner except that lactose was used instead of heavy magnesium carbonate and stored under the same conditions.

Compound	Additive		Changes in appearance after 1 week at 50°C and 75% RH
Compound (A)	Invention:	Heavy magnesium carbonate	-
	Control:	Lactose	++
Omeprazole	Invention:	Heavy magnesium carbonate	-
	Control:	Lactose	++
Timoprazole	Invention:	Heavy magnesium carbonate	-
	Control:	Lactose	++
Compound (C)	Invention:	Heavy magnesium carbonate	-
	Control:	Lactose	++
Compound (D)	Invention:	Heavy magnesium carbonate	-
	Control:	Lactose	++

Notes: - : No changes

++ : Severely

As is evident from the above results, the pharmaceutical compositions of the invention were all stable whether the active ingredient was the compound (A), omeprazole, timoprazole, the compound (C) or the compound (D).

Experimental Example 3

Pharmaceutical compositions were produced in the same manner as in Examples 3 and 5 except that different basic inorganic Mg or Ca salts were used or that lactose was used as a control, and Example 7. After storage at 50°C and 75% RH for I week or at 40°C for 6 months, the compositions were observed for changes in appearance and for active ingredient content (residual percentage).

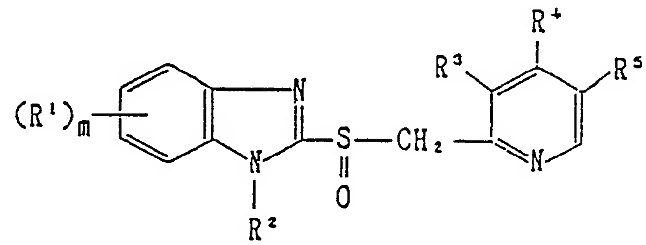
Table 2

Additive				Initial	50°C, 75% RH, 1 week	40°C, 6 months
Tablets made by the procedure of Example 3						
Invention	Heavy magnesium carbonate	Appearance		White	No change	No change
		Content		100%	98.0%	99.5%
	Precipitated calcium carbonate	Appearance		White	No change	No change
		Content		100%	97.4%	96.5%
	Magnesium silicate	Appearance		White	No change	No change
		Content		100%	94.5%	95.0%
Control	No addition (lactose)	Appearance		Pale violet	Dark violet	Dark violet
		Content		100%	73.5%	82.1%
Granu les made by the procedure of Example 5						
Invention	Heavy magnesium carbonate	Appearance		White	No change	No change
		Content		100%	98.2%	99.1%
	Precipitate calcium carbonate	Appearance		White	No change	No change
		Content		100%	97.2%	98.6%
	Magnesium oxide	Appearance		White	No change	No change
		Content		100%	99.4%	99.0%
Control	No addition (lactose)	Appearance		Pale violet	Dark violet	Dark violet
		Content		100%	84.2%	89.4%
Capsules of Example 7						
Invention	Heavy magnesium carbonate	Appearance		White	No change	No change
		Content		100%	98.4%	99.1%

The above results clearly indicate that the compositions of the invention show no changes in appearance at all and are stable in terms of the active ingredient content.

Claims

1. A pharmaceutical composition which comprises a compound of the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, akylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4, and a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium.

2. A pharmaceutical composition as claimed in claim 1, wherein the compound is 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

3. A pharmaceutical composition as claimed in claim 1, wherein the compound is 2-[[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-2-pyridyl]methylsulfinyl]benzimidazole.

4. A pharmaceutical composition as claimed in claim 1, wherein the compound is 2-[(4-propoxy-2-pyridyl)methylsulfinyl]benzimidazole.

5. A pharmaceutical composition as claimed in claim 1, wherein the compound is 2-[(3-methyl-4-propoxy-2-pyridyl)methylsulfinyl]benzimidazole.

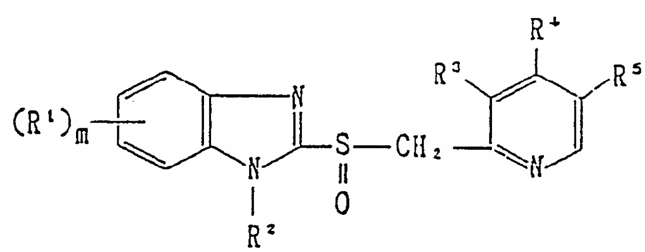
6. A pharmaceutical composition as claimed in claim 1, wherein the compound is 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfinyl]benzimidazole.

7. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of magnesium is magnesium carbonate.

8. A pharmaceutical composition as claimed in claim 1, wherein the basic inorganic salt of calcium is precipitated calcium carbonate.

9. A pharmaceutical composition as claimed in claim 1, wherein the composition is in particles and enteric-coated.

10. A method of producing a stabilized pharmaceutical composition which comprises incorporating a basic inorganic salt of magnesium and/or a basic inorganic salt of calcium in a pharmaceutical composition containing a compound of the formula



wherein R^1 is hydrogen, alkyl, halogen, cyano, carboxy, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl, acyl, carbamoyloxy, nitro, acyloxy, aryl, aryloxy, alkylthio or alkylsulfinyl, R^2 is hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl or alkylsulfonyl, R^3 and R^5 are the same or different and each is hydrogen, alkyl, alkoxy or alkoxyalkoxy, R^4 is hydrogen, alkyl, alkoxy which may optionally be fluorinated, or alkoxyalkoxy, and m is an integer of 0 through 4.

11. The use of a pharmaceutical composition for the manufacture of an antiulcer agent.

ELKINGTON AND FIFE

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OUR REFERENCE
JJL/002/PB/5164E

YOUR REFERENCE

2nd July, 1987.

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REGISTERED MAIL.

Dear Sirs,

Re: European Patent Appln. No. 87 301244.7
TAKEDA CHEMICAL INDUSTRIES, LTD.

We thank you for your letter of 9th June, 1987, with the suggested title. This is in principle acceptable, but we think, with respect, that the title should be extended to refer to the use of the pharmaceutical compositions of the invention as antiulcer agents. Accordingly, we suggest the following title:

"Stabilized pharmaceutical composition comprising a benzimidazole compound, its production and its use as an antiulcer agent".

In reviewing the application in connection with the title, we noticed a clerical error in Claim 11 which clearly was intended to refer to preceding claims since it is not meaningful as it stands.

We, accordingly, ask that Claim 11 should be amended by the insertion after the words "..a pharmaceutical composition" of the words "according to any of Claims 1-9". A photostat of page 40 on which the desired amendment is indicated in manuscript is attached. We also file herewith in triplicate a new page 40 incorporating this amendment only.

In our respectful submission, the need for such amendment and its basis in the application are self-evident. We, accordingly, respectfully ask for the necessary action to be taken.

Yours faithfully,

Encs.

J. J. LAREDO
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(54) **Pharmaceutical formulations of acid labile substances for oral use.**

(57) Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

EP 0 244 380 A2

Pharmaceutical formulations of acid labile substances for oral use

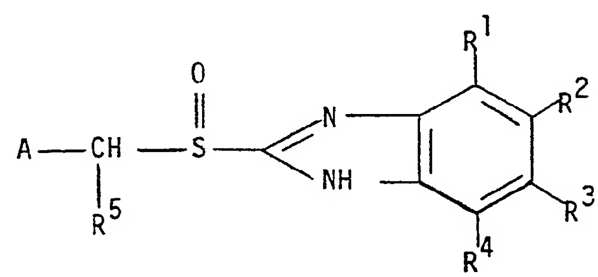
Field of the Invention

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, to a method for the manufacture of such preparations and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

Background of the Invention

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



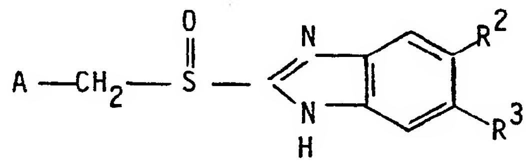
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4 are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole.

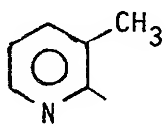
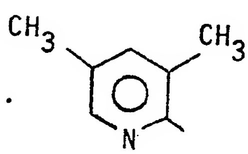
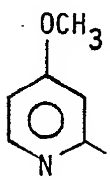
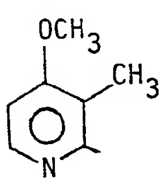
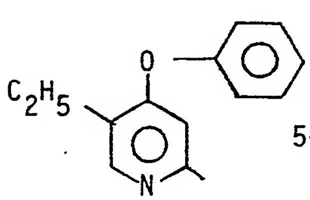
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-85850258,6, EP-A1-0 080 602, EP-0127 736, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di--methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the $H^{+}K^{+}$-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of $H^{+}K^{+}$-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

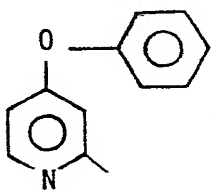
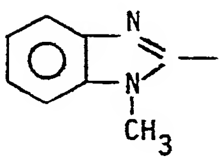
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620

Cont.

Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+--ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidily decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a

combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

Outline of the invention

According to the present invention it has been found that the known acid labile compounds with the general formula I above in which R^1, R^2, R^3 and R^4 are the same or different and are

(a) hydrogen

(b) halogen, e.g. F, Cl, Br, I

(c) -CN

(d) -CHO

(e) $-CF_3$

(f) $-\overset{O}{\overset{\|}{C}}-R^{11}$

(g) $-O-C-R^{12}$

(h) $-CH(OR^{13})_2$

(i) $-(Z)_n-B-D$

(j) aryl containing up to 10 carbon atoms

(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms

(l) -alkylthio containing 1-6 carbon atoms

(m) $-NO_2$

(n) -alkylsulfinyl containing 1-6 carbon atoms

(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups

($-\overset{O}{\overset{\|}{C}}-$), whereby if R^1 and R^2, R^2 and R^3 or R^3 and

R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxy containing 1-4 carbon atoms
(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is (a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is $-O-$ or $-\overset{\overset{\large O}{\|}}{C}-$;

n is 0 or 1;

B is (a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms

(c) alkenylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c) $-\overset{O}{\overset{\|}{C}}-R^9$
(d) $-(Y)_m-(\overset{O}{\overset{\|}{C}})_r-R^{10}$

wherein

R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

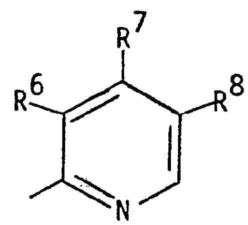
Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;

R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or
(b) alkyl containing 1-6 carbon atoms;

R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(h) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

-CH=CH-CH=CH-

$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$

-O-CH=CH-

-NH-CH=CH-

$-N(CH_3)-CH=CH-$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2- (4-methoxy-3,5 dimethyl- -2-pyridinyl methyl sulfinyl -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethyl-aminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good

stability of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Detailed description of the invention

Cores

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as

aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3\ 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium etc. salts of acid labile compounds,either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3,4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrollidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or the like. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

<u>Enteric coating layer</u>

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the

trade name Eudragit^R L 12,5 or Eudragit^R L 100,(Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit^R L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex^R (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

<u>Final dosage form</u>

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin

capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the vovel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1 - 3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253	g
	Lactose anhydrous	167	g
	Hydroxypropyl cellulose	25	g

II	Compound 1, Table I	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	125 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methyl-cellulose	20 g
	Distilled water	400 g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table I.

Uncoated pellets

I	Compound 2, Table I sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g
	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
V	Hydroxypropyl methylcellulose phthalate	57	g
V	Cetyl alcohol	3	g
V	Acetone	540	g
V	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite $[Al_2O_3.6MgO.CO_2.12H_2O]$	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

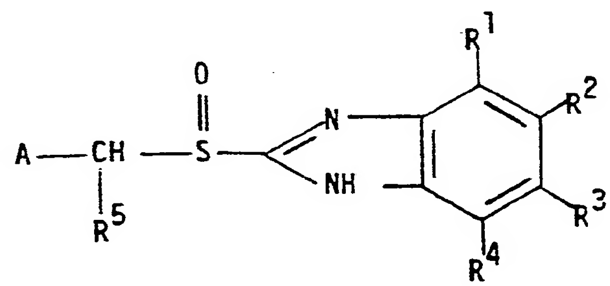
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

CLAIMS

1. An oral, pharmaceutical preparation containing an acid labile compound as the active ingredient characterized in that it is composed of core material containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{O}{\overset{\|}{C}}-$lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n not is an integer and less than two.

4. A preparation according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A preparation according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A preparation according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A preparation according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A preparation according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

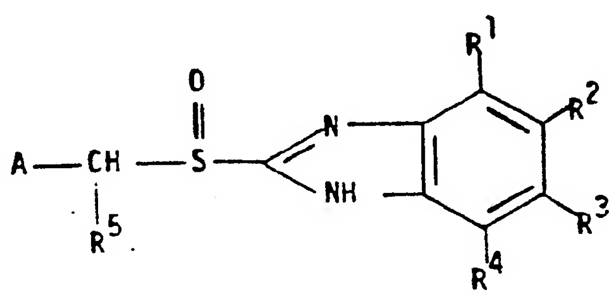
12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

13. Use of the preparation according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

CLAIMS FOR THE CONTRACTING STATES AT, ES, GR.

1. A process for the preparation of an oral, pharmaceutical formulation containing an acid labile compound as the active ingredient characterized in that the cores containing the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{\overset{O}{\parallel}}{C}-$lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl] -benzimidazole.

3. A process according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite

substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n not is an integer and less than two.

4. A process according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A process according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A process according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A process according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A process according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A process according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A process according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A process according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

12. Use of the formulation prepared according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

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(54) **New pharmaceutical preparation for oral use.**

(57) Pharmaceutical preparation containing omeprazole together with an alkaline compound or an alkaline salt of omeprazole optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

EP 0 247 983 A2

New pharmaceutical preparation for oral use

Field of the Invention

The present invention is related to a new stable pharmaceutical preparation containing omeprazole for oral use, to a method for the manufacture of such a preparation and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

Background of the Invention

From e.g. EP-A1-0 005 129 omeprazole, 5-methoxy-2(((4-methoxy-3,5--dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, a potent inhibitor of gastric acid secretion is known. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov 27, 1982, p. 1223-1224) and can be used for the treatment of gastric and duodenal ulcers. Omeprazole is however susceptible to degradation/transformation in acid reacting and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values the degration reaction proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture and organic solvents.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

In human pharmacological studies it was found that the rate of release of omeprazole from a pharmaceutical dosage form can influence the total

extent of absorption of omeprazole to the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal.

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

An enteric coated dosage form of omeprazole was reported by Pilbrant and Cederberg, in the above cited Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120. The publication describes a conventional enteric coated dosage form and states that it has an acceptable storage stability - for clinical studies. It was later found that the stability of this dosage form was insufficient during long-term storage required for a marketed pharmaceutical dosage form.

If a conventional formulation of omeprazole is made, the stability is

not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

In DE-A1-3046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of omeprazole in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing omeprazole since direct contact between substances such as cellulose acetate phthalate (CAP) and omeprazole causes degradation and discolouration of omeprazole.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of omeprazole in gastric juice.

DE-A1-1 204 363 describes a tree-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for omeprazole, where a rapid release of the drug in the small intestine is needed.

DE-A1 12 04 363 describes coating with three layers to achieve release

of a drug in the ileum, an aim which is outside the scope of the present invention.

GB-A-1 485 676 describes a way to obtain a preparation, which effervesces in the small intestine, by enteric coating a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. The formulation cannot be adopted for a pharmaceutical dosage form containing omeprazole, as the presence of an acid in contact with omeprazole in the cores would give a result that omeprazole was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixted with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for omeprazole where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing omeprazole.

Outline of the invention

The object of the present invention is to provide an enteric coated dosage form of omeprazole, which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing omeprazole mixed with alkaline compounds or an alkaline salt of omeprazole optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water o rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low

level in order to obtain a good stability of the dosage form during long-term storage.

Detailed description of the invention

Cores

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of omeprazole such as the sodium, potassium, magnesium, calcium etc. salts of omeprazole, which are described in e.g. EP-A2-124 495, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, tablets, hard gelatine or soft gelatine capsules by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO.CO_2 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, polyvinyl acetal diethyl-aminoacetate or the like. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

In case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit® L 12,5 or Eudragit® L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing omeprazole mixed with an alkaline reacting compound or cores containing an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound. The alkaline reacting core material and/or alkaline salt of the active ingredient, omeprazole, enhance the stability of omeprazole. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with an inert reacting water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and/or the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing omeprazole (enteric coated tablets, capsules or pellets) is kept low, preferably not more than 1.5 % by weight. As a consequence the final package containing hard gelatin capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the gelatin shell to a level where the water content of the enteric coated pellets filled in the capsules does not exceed 1.5 % by weight.

Process

A process for the manufacturer of the oral dosage form represents a further aspect of the invention. After the forming of the cores the

cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-400 mg of omeprazole. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

The effect of different magnesium compounds was evaluated in the form of enteric coated tablets. Tablet cores were first made by known techniques according to the formulations listed in Table 1, followed by application of separating layers and enteric coating layers as shown in Table 2.

Table 1 Formulations for the tablet cores (mg)

Formulations No.	1	2	3	4	5	6	7
Omeprazol	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Lactose	134.0	119.0	119.0	119.0	118.8	118.5	119.0
Hydroxypropyl cellulose (low substitution	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropyl cellulose	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Na_2HPO_4	-	15.0	-	-	0.2	-	-
Na lauryl sulfate	-	-	-	-	-	0.5	-
MgO	-	-	15.0	-	-	-	-
$Mg(OH)_2$	-	-	-	15.0	15.0	15.0	-
Synthetic hydrotalcite $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O]$	-	-	-	-	-	-	15.0
Total	160.0	160.0	160.0	160.0	160.0	160.0	160.0

Table 2 Formulations for coatings (mg)

Formulation No.	I	II	III	IV
Separating layer (inner):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Magnesium hydroxide	-	-	0.3	-
Synthetic hydrotalcite	-	-	-	0.3
Separating layer (outer):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Enteric coating layer:				
Hydroxypropyl methylcellulose phthalate	7.0	7.0	7.0	7.0
Cetyl alcohol	0.5	0.5	0.5	0.5

The tablets thus obtained were stored in open form under so called accelerated conditions, that is 40°C, and 75 % relative humidity, and the changes in appearance with the passage of time were observed. Storage for six months under these conditions corresponds to storage at normal temperature for three years. This means that high stability sufficient for paractical use may be assured if a drug remains intact for about one week under the mentioned conditions. The result is summerized in Table 3. As may be seen from the table, a remarkable stabilizing effect is achieved when a magnesium compound is contained in the inner separating layer.

Table 3 Stabilizing Effect (Appearance of Preparations)

Coating Layer		Core material 1	2	3	4	5	6	7
I	At the start	C	A	A	A	A	A	A
	60°C; after 7 days	E	D	C	C	C	C	D
	40°C; 75 % RH; after 7 days	F	E	B	B	B	B	E
II	At the start	A	A	A	A	A	A	A
	60°C; after 7 days	E	B	A	A	A	A	C
	40°C; 75 % RH; after 7 days	E	D	A	A	A	A	D
III	At the start	A	A	A	A	A	A	A
	60°C; after 15 days	B	A	A	A	A	A	A
	40°C; after 30 days	A	A	A	A	A	A	A
	40°C; 75 % RH; after 15 days	B	A	A	A	A	A	A
IV	At the start	A	A	A	A	A	A	A
	60°C; after 15 days	B	A	A	A	A	A	A
	40°C; after 30 days	A	A	A	A	A	A	A
	40°C; 75 % RH; after 15 days	B	A	A	A	A	A	A

A: white, B: brownish white, C: faint brown, D: light brown, E: brown, F: deep brown.

All the samples evaluated as A (white) in the above table showed no descoloration even on split surfaces. The samples evaluated as B (brownish white) showed little change in appearance, but some discoloration was observed on split surfaces.

Table 4 shows the result of a stability test on the omeprazole preparation according to Example 1 (Formulation No 4-IV). The formulation was stored in a closed glass bottle at room temperature for the indicated period of time. This clearly demonstrates that preparations with unusually high stability were obtained.

Table 4 Stability of enteric coated omeprazole preparations (Tablets of Formulation No. 4-IV)

Storage Period	Appearance	Omeprazole Content (%)
At the start of test	White	100.0
1 year at room temperature	White	99.9
2 years at room temperature	White	100.0

Example 2

Uncoated pellets

I	Mannitol powder	16 150 g
	Lactose anhydrous	800 g
	Hydroxypropyl cellulose	600 g
	Microcrystalline cellulose	400 g

II	Omeprazole	2 000 g
	Sodium lauryl sulphate	50 g
	Disodium hydrogen phosphate	80 g
	Distilled water	4 400 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

III	Uncoated omeprazole pellets	6 000 g
	Hydroxypropyl methylcellulose	240 g
	Distilled water	4 800 g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric-coated pellets

	Subcoated pellets	500 g
IV	Hydrozypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 225 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

Example 3

This example illustrates that a variety of polymers can be used for subcoating, e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols.

Uncoated pellets

I	Mannitol powder	1 620 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Sodium lauryl sulphate	1.0 g
	Disodium hydrogen phosphate	9.3 g
	Distilled water	515 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

III	Uncoated omeprazole pellets	500 g
	Polyvinylpyrrolidone	20 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric-coated pellets

IV	Subcoated pellets	500 g
	Hydroxypropyl methyl-cellulose phthalate	45 g
	Cetyl alcohol	5 g
	Acetone	219 g
	Ethanol	680 g

The enteric-coated pellets were prepared as described in Example 2.

Example 4

Uncoated pellets

I	Mannitol powder	1 610 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g

II	Omeprazole	200 g
	Pluronic F68	10 g
	Disodium hydrogen phosphate	24 g
	Distilled water	450 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

		Uncoated pellets	500 g
III	{	Polyvinylpyrrolidone	30 g
		Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric coated pellets

		Subcoated pellets	500 g
IV	{	Hydroxypropyl methylcellulose phthalate	45 g
		Cetyl alcohol	5 g
		Methylene chloride	371 g
		Ethanol	680 g

The enteric coated pellets were prepared as described in Example 2.

Example 5

This example illustrates that a variety of polymers can be used as enteric coating material e.g. cellulose acetate phthalate, poly-(vinyl acetate/vinyl alcohol phthalate), hydroxypropyl methylcellulose phthalate, poly-(methacrylic acid/methacrylic acid methyl esters), poly-(acrylic acid/methacrylic acid methyl esters). The polymers can be applied with/without plasticizer, e.g. polyethylene glycols, triacetin, dimethyl polysiloxan, Citroflex®, cetyl alcohol, stearyl alcohol, diethyl phthalate.

Enteric-coated pellets can also be manufactured from water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit® L 100-55, Coating CE 5142 (BASF).

Uncoated pellets

I	Lactose powder	277 g
	Lactose anhydrous	118 g
	Hydroxypropyl cellulose	25 g
	Colloidal silica	25 g
II	Omeprazole	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	2 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	170 g

The uncoated pellets were prepared as described above.

Subcoated pellets

The uncoated pellets were subcoated as described in Example 2.

Enteric coated pellets

	Subcoated pellets	500 g
III	Eudragit L 100	45 g
	Stearyl alcohol	4.5 g
	Ethanol	1 320 g

The enteric coated pellets were prepared as described above.

Example 6

Formulations with the sodium salt of omeprazole.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 2 with the exception that the omeprazole sodium salt was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g
	Pellets subcoated with III	500 g
IV	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500 g
V	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 2.

Example 7 and 8

Formulations with the magnesium salt of omeprazole.

Uncoated pellets

		Example No 7	8
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1 673 g	1 473 g
	Microcrystalline cellulose	100 g	100 g
	Magnesium hydroxide	-	200 g
II	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole magnesium salt was added together with the other ingredients in mixture I.

Subcoated pellets

		Example 7 and 8
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

Enteric coated pellets

		Examples 7 and 8
	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
IV	Cetyl alcohol	3 g
IV	Acetone	540 g
IV	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example 9 and 10

Manufacture of tablets.

Tablet cores

		Examples No 9	10
I	Omeprazole	400 g	-
I	Omeprazole sodium salt, corresponding to omeprazole 400 g	-	426 g
I	Lactose, anhydrous	1 420 g	1 409 g
I	Polyvinylpyrrollidone, crosslinked	100 g	100 g
I	Sodium carbonate, anhydrous	15 g	-
II	Methyl cellulose	12 g	12 g
II	Distilled water	200 g	200 g
	Magnesium stearate	30 g	30 g

The powder mixture I was carefully homogenized and granulated by the solution II. The wet mass was dried in a fluidized bed dryer using an inlet air temperature of +50°C for 30 minutes. The dried mixture was then forced through a sieve with an apperture of 0.5 mm. After mixing with magnesium stearate the granulate was tableted on a tableting

machine using 6 mm punches. The tablet weight was 100 mg.

Subcoating

The tablets containing omeprazole were subcoated with approximately 10 % by weight of hydroxypropyl methylcellulose from a water solution using a perforated coating pan apparatus.

The tablets containing omeprazole sodium salt were subcoated using the dry coating technique. A tablet granulate containing

Lactose anhydrous	4 000 g
Polyvinylpyrrolidone, (PVP)	180 g
Ethanol 95 %	420 g
Magnesium stearate	42 g

was prepared in the following way. The lactose was granulated with a solution of PVP in ethanol and dried. After drying magnesium stearate was admixed.

The granulate mass was dry coated around the tablet cores of example 9 using a Manesty Dry Cota[R] tableting machine. The tablet weight of the dry coated tablets was 475 mg. Each tablet contained 20 mg of omeprazole.

Enteric coating

The subcoated tablets obtained above were enteric coated using the same coating solution:

Hydroxypropyl methylcellulose phthalate	1 500 g
Cetyl alcohol	105 g
Methylene chloride	15 000 g
Isopropanol	15 000 g
Distilled water	3 150 g

The coating was applied in a perforated coating pan apparatus. An approximate amount of one kg of coating solution was applied for each kg of tablets.

COMPARATIVE EXAMPLES

Examples I, II and III

These examples illustrate that the buffer salt used effects the enteric-coated omeprazole pellets properties when the sub-coating layer is absent. A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellets shows inferior acid resistance properties. C.f. also the Example 4 above.

Uncoated pellets		Examples No I	II	III
I	Mannitol powder	1 610 g	1 610 g	1 610 g
	Lactose anhydrous	80 g	80 g	80 g
	Hydroxypropyl cellulose	60 g	60 g	60 g
	Microcrystalline cellulose	40 g	40 g	40 g
II	Omeprazole	200 g	200 g	200 g
	Pluronic F68	10 g	10 g	10 g
	Disodium hydrogen phosphate	2 g	8 g	24 g
	Distilled water	450 g	450 g	450 g

The uncoated pellets were prepared as described in Example 2 above.

Enteric coated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The coated pellets were prepared as described in Example 2 above.

Example IV

This formulation is the same as in Example 6 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 6.

Enteric-coated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The enteric coated pellets were prepared as described in Example 2.

Example V

This formulation is the same as in Example 8 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole magnesium salt	222	g
	Mannitol powder	1 473	g
	Microcrystalline cellulose	100	g
	Magnesium hydroxide	200	g
II	Sodium lauryl sulphate	5	g
	Distilled water	375	g

The preparation was made as described in Example 8.

Enteric coated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The pellets were prepared as described in Example 2 above.

Properties of the enteric coated pellets

For the preparations according to Examples 2-8 and comparative Examples I-V above one or both of the following studies have been performed.

Acid resistance

The following resistance of the formulations was studied in the following way: The formulations were added to gastric fluid USP (without enzyme), 37°C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulations was determined.

Rate of dissolution in buffer solution

In order to establish the rate of dissolution in the small intestine, the formulations were added to a buffer solution. Buffer solution 37°C, USP dissolution apparatus No 2 (paddle), 100 r/min. After 10 or 30 minutes the amount of omeprazole dissolved was determined. The results are presented in the following Table 5.

Table 5

Example No	Omeprazole content mg/g	Acid resistance, amount intact omeprazole (%) after 2 hours	% dissolved omeprazole at different pH:s and after 10 or 30 min %	pH	min
2	89.2	95	100	6.8	10
3	90	96	91	6.0	10
4	88	89	*)		
5	82	93	70	7.5	30
6	81.3	87	93	6.8	10
7	91	95	**)		
8	89	98	**)		
I	93	97	*)		
II	92	94	*)		
III	94	58	*)		
IV	86.5	4			
V	91	93	**)		

*) The stability of the formulation was studied during storage in glass bottles also containing a desiccant device. After one month storage at +50°C the formulation according to Example 4 was virtually intact with no change in appearance or physicochemical characteristics. Pellets according to Example I and II turned brown due to degradation, while the pellets according to Example III retained to original white colour.

**) The formulations according to Examples 7 and 8 were white and not affected by the coating process. The enteric coated pellets according to Example V, where the enteric coating was applied directly on the cores according to Example 8, was discoloured already during the enteric coating process.

Further comparative test

This example demonstrates the effect of the moisture content of the preparations according to the invention on storage stability.

The stability of omeprazole pellets according to the invention was compared with that of omeprazole pellets with higher water content. Omeprazole pellets were prepared according to the invention with a water content of 1 %. Two other portions of the same formulation were conditioned to a water content of 2 % and 5 % respectively. The three formulations, packed in tight containers not contining a desiccant, were stored for one month at +50°C. After this time the packages were opened and the pellets were assayed for the amount of omeprazole by HPLC. The formulation according to the invention had an omeprazole content of 98.5 % of the initial value. The other two formulations with a water content of 2 and 5 % respectively were virtually totally degraded and had only trace amounts of intact omeprazole.

DISCUSSION

From the results given in Table 5 it can be seen that formulations containing omeprazole with acceptable acid resistance can be prepared by using a conventional enteric coating technique (see for instance Examples I, II and V). However, it is also obvious that the storage stability of the formulations according to Examples I, II and V is not acceptable, since a discolouration, showing a degradation of omeprazole, occours during short storage at an elevated storage temperature (Examples I and II) or already during the enteric coating process (Example V).

If the amount of alkaline substances in the cores is increased to a level where omeprazole has an acceptable storage stability (Example III) or if an alkaline reacting salt of omeprazole is used in the preparation of the cores (Example IV), then, without the separating layer of the invention, the resistance to dissolution in acid media becomes unacceptably low and much or all of the active substance will degrade already in the stomach and thus, it has no effect on the gastric acid

secretion.

When the preparation is carried out according to the inventon as for instance in Example 4, a good resistance towards gastric juice as well as a good stability during long-term storage is obtained. This is in contrast with the formulations in Examples I, II and III where either an acceptable acid resistance or an acceptable storage stability can be achieved - but not both. The same comparison can be made between the formulations according to Examples 7 and 8 according to the invention and the formulation according to Example V, where the separating layer was omitted. Examples 7 and 8 differ in that a buffering substance, magnesium hydroxide, has been included in the cores of Example 8. This further improves the acid resistance as well as the storage stability of Example 8 in comparison with Example 7.

The further comparative test shows the great importance of a low water content in the preparations.

Thus in order to prepare pharmaceutical formulations of omeprazole for oral use, which exert good stability during long-term storage as well as good stability during the residence in the stomach after administration, the preparation is made in the following way:

a) Omeprazole together with an alkaline reacting compound or compounds or an alkaline reacting salt of omeprazole optionally mixed with alkaline reacting compound are inclunded in the core material.

b) The core material is subcoated with one or more inert, in water soluble or in water rapidly disintegrating layers, which separate the alkaline reacting core from the enteric coating. The subcoating layer may optionally contain pH-buffering compounds.

c) The subcoated cores are coated with an acid insoluble enteric coating, optionally containing plasticizers.

Biopharmaceutical studies

The hard gelatin capsules according to Example 2 were administered to 12 healthy, young male volunteers in the following way:

The volunteers came to the laboratory in the morning after having abstained from food since 10 p.m. the night preceeding the experimental day. A zero time blood sample was taken. One omeprazole capsule according to Example 2 was administered together with 150 ml of tap water. Further blood samples were taken during the day.

In another experiment the same volunteers were administered 20 mg of omeprazole in the form of a suspension of micronized omeprazole in a sodium bicarbonate water solution. In order to reduce the degradation of omeprazole in the stomach to a minimum, sodium bicarbonate solution was given to the subjects just before the administration of the omeprazole suspension and at further four times with a 10-minutes interval after the drug intake. The concentration of omeprazole in blood plasma was assayed by high pressure liquid chromatography (Persson, Lagerström and Grundevik. Scand J Gastroenterol 1985, 20, (suppl 108), 71-77. The mean plasma concentrations are given in Table 6.

Table 6

The plasma concentrations (µmol/l) after 20 mg single oral doses of omeprazole given as hard gelatin capsules according to Example 2 and as a suspension of micronized omeprazole in sodium bicarbonate solution.

Time (min)	Capsules	Suspension
10		0.84
20		0.90
30	0.03	0.84
45		0.64
60	0.22	0.44
90	0.36	0.24
120	0.39	0.13
150	0.29	
180	0.20	0.04
210	0.10	
240	0.05	0.01
300	0.02	0
360	0.01	
420	0	

Although the plasma concentration peak at different times, the two formulations are bioequivalent. The mean relative bioavailability of the capsules in comparision with the suspension was 85 % +23 % (S.D.). The comparison was based on the total area under individual plasma concentration versus time curves.

Thus, by preparing capsules according to the invention it is possible to obtain a preparation with the same bioavailability as a suspension containing the same amount of micronized active compound. It is, however, to be noticed that when the suspension is administered, the patients must also be given sodium bicarbonate solution frequently in order to minimize pre-absorption degradation of omeprazole in the stomach.

CLAIMS

1. An oral, pharmaceutical preparation containing omeprazole as the active ingredient characterized in that it is composed of core material containing omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O]$, wherein n is not an integer and less than 2.

3. A preparation according to claim 1 wherein the subcoating comprises two or more sub-layers.

4. A preparation according to claim 3 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

5. A preparation according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12.

6. A preparation according to claim 5 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, where n is not an integer and less than 2.

7. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of omeprazole such as the sodium, potassium, magnesium, calcium or ammonium salt.

8. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of omeprazole mixed with an inert, alkaline compound.

9. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

10. A preparation according to claim 1 wherein the water content of the final dosage form containing omeprazole does not exceed 1.5 % by weight.

11. Process for the preparation of an oral pharmaceutical formulation containing omeprazole in which cores containing omeprazole mixed with an alkaline reacting compound or compounds or an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating.

12. Use of the preparation according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

CLAIMS FOR THE CONTRACTING STATES AT, ES, GR.

1. A process for the preparation of an oral, pharmaceutical formulation containing omeprazole as the active ingredient characterized in that the cores containing omeprazole mixed with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $[Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O]$, wherein n is not an integer and less than 2.

3. A process according to claim 1 wherein the subcoating comprises two or more sub-layers.

4. A process according to claim 3 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

5. A process according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12.

6. A process according to claim 5 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, where n is not an integer and less than 2.

7. A process according to claim 1 wherein the alkaline core comprises an alkaline salt of omeprazole such as the sodium, potassium, magnesium, calcium or ammonium salt.

8. A process according to claim 7 wherein the alkaline core comprises an alkaline salt of omeprazole mixed with an inert, alkaline compound.

9. A process according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

10. A process according to claim 1 wherein the water content of the final dosage form containing omeprazole does not exceed 1.5 % by weight.

11. Use of the formulation prepared according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

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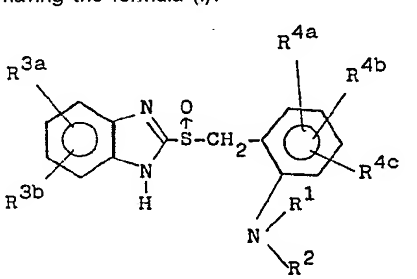
(54) Stabilized benzimidazole derivative and composition.

(57) A stabilized physiologically active benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group. The stabilized benzimdazole derivative is in amorphous form or present in contact with a basic material.

EP 0 248 634 A2

Description

STABILIZED BENZIMIDAZOLE DERIVATIVE AND COMPOSITION

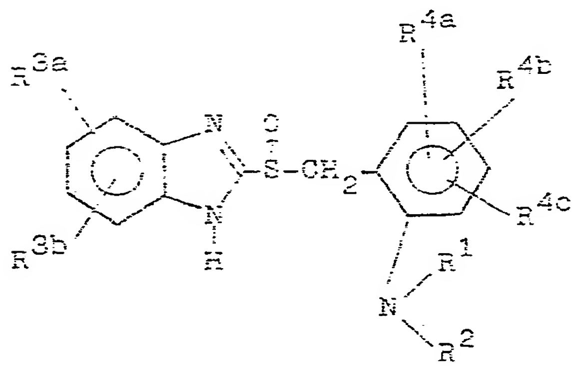
BACKGROUND OF THE INVENTION

Field of the invention

This invention relates to a stabilized benzimidazole derivative and a composition in which a benzimidazole derivative is stabilized.

Description of prior art

There is known a physiologically active benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

The benzimidazole derivative of the formula (I) shows a prominent inhibitory action on secretion of gastric acid as is described in GB 2,161,160A and GB 2,163,747A (corresponding to DE 3,531,487A1). Moreover, some benzimidazole derivtives of the formula (I) can be employed as cytoprotective agents for gastrointestinal tract.

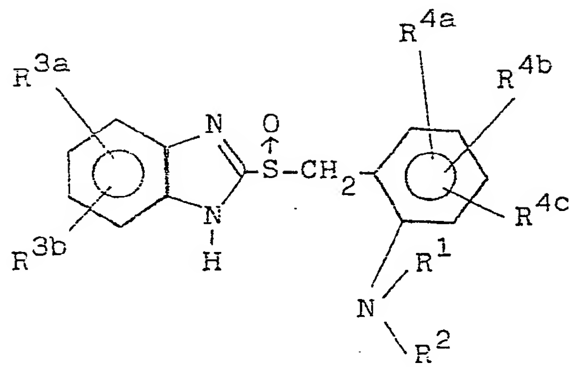
SUMMARY OF THE INVENTION

The present inventors have made study for acturally utilizing the benzimidazole derivative of the formula (I) as a physiologically active component of a pharmaceutical and found that these benzimidazole derivative is poor in storage stability.

Accordingly, an object of the present invention is to provide a physiologically active benzimidazole derivative of the formula (I) which is improved in storage stability.

Another object of the invention is provide a composition containing a physiologically active benzimidazole derivative under stabilized condition.

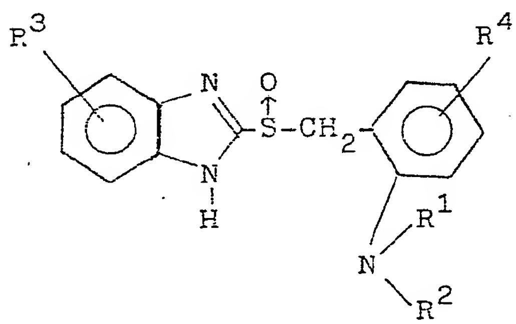
There is provided by the present invention a physiologically active benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group,
which is in amorphous state or is kept in contact with an organic or inorganic basic material.

Particularly, the present invention provides a stabilized physiologically active benzimidazole derivative of the formula (II):

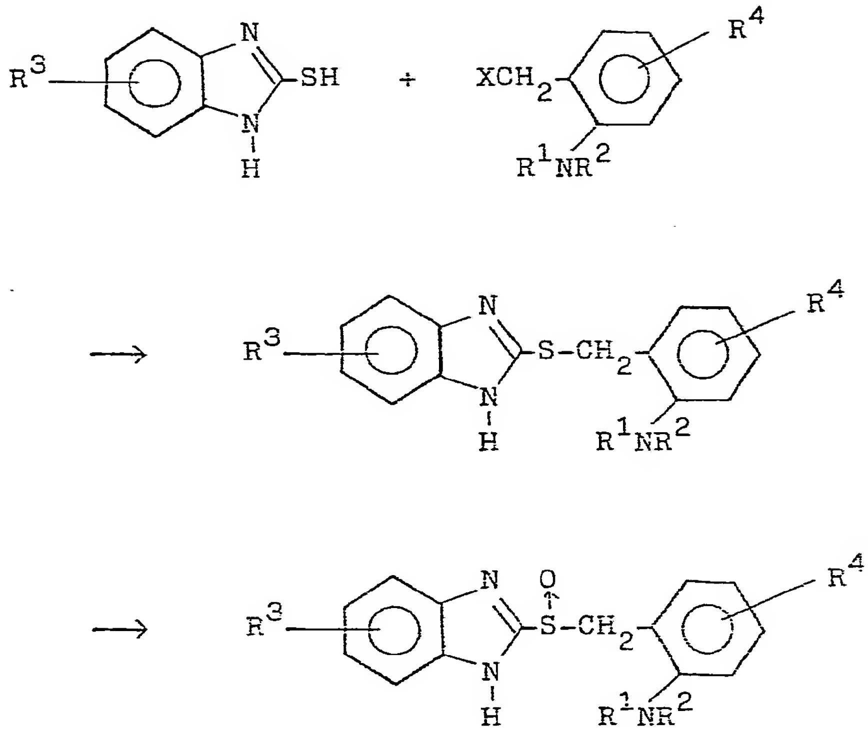


(II)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^3 and R^4 independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, which is in amorphous state or is kept in contact with an organic or inorganic basic material.

DETAILED DESCRIPTION OF THE INVENTION

The benzimidazole derivatives of the formula (I) can be prepared by known processes. For instance, the benzimidazole derivative of the formula (II) can be prepared by the process according to the following equation:



wherein X is a reactive group and each of R^1, R^2, R^3 and R^4 has the same meaning as defined hereinbefore. The benzimidazole derivatives of the formula (I) other than the derivative of the formula (II) can be prepared in similar manners.

Representative examples of the compounds of the formula (I) include:

Compound 1: 2-(2-dimethylaminobenzylsulfinyl)benzimidazole,
Compound 2: 2-(2-diethylaminobenzylsulfinyl)benzimidazole,
Compound 3: 2-(2-aminobenzylsulfinyl)benzimidazole,
Compound 4: 2-(2-methylaminobenzylsulfinyl)benzimidazole,
Compound 5: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxybenzimidazole,
Compound 6: 2-(2-diethylaminobenzylsulfinyl)-5-methoxybenzimidazole,
Compound 7: 2-(2-dimethylamino-6-methylbenzylsulfinyl)benzimidazole,
Compound 8: 2-(2-dimethylaminobenzylsulfinyl)-5-methoxycarbonylbenzimidazole,
Compound 9: 2-(2-dimethylaminobenzylsulfinyl)-5-methylbenzimidazole,
Compound 10: 5-chloro-(2-dimethylaminobenzylsulfinyl)benzimidazole,
Compound 11: 5-amino-(2-dimethylaminobenzylsulfinyl)benzimidazole,
Compound 12: 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole,
Compound 13: 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole,
Compound 14: 2-(2-piperidinobenzylsulfinyl)benzimidazole,
Compound 15: 2-[2-(N-cyclohexyl-N-methylamino)benzylsulfinyl]benzimidazole, and
Compound 16: 2-[2-(N-benzyl-N-methylamino)benzylsulfinyl]benzimidazole.

The benzimidazole derivative employed in the present invention preferably is a compound having the formula (I) wherein R^1 is an alkyl group containing 1-8 carbon atoms. R^2 preferably is a lower alkyl group. Preferably, each of R^{3a} and R^{3b} is independently hydrogen atom or an alkoxy group. Preferably, each of R^{4a}, R^{4b} and R^{4c} is independently is hydrogen atom or a lower alkyl group. In the specification, the lower alkyl group and the lower alkoxy group mean those containing 1-6 carbon atoms.

As a result of the study of the present inventors, it has found that the benzimidazole derivative of the formula (I), which is prepared in the form of crystals according to known processes for the preparation, can be prominently improved in storage stability when it is formed in amorphous state.

The benzimidazole derivative of the formula (I) can be converted into a amorphous compound, for instance, by freezing a crystalline compound in an organic solvent and then evaporating the solvent. However, it is advantageous to treat the crystalline compound in such a manner that the crystalline compound is dissolved in an organic solvent containing an organic polymer and then forcing to remove the solvent through evaporation or that the crystalline compound is dissolved in an organic solvent containing an organic polymer and then spray-drying the resulting solution.

In the above process, there is no need of dissolving the benzimidazole derivative and/or the organic polymer

in the solvent. For instance, the benzimidazole derivative and/or organic polymer can be suspended in the organic solvent. For this reason, the organic solvent can be replaced with an aqueous organic solvent or replaced simply with water. In the case that water or an aqueous organic solvent is employed as the solvent, the organic polymer preferably is water-soluble. Further, in the case that water or an aqueous organic solvent is utilized, a surface active agent can be utilized as a dispersant.

Examples of the organic polymers employable for converting a crystalline benzimidazole derivative into an amorphous benzimidazole derivative include synthetic or natural polymers such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic, α-starch, oxidized starch, heat-treated starch, enzyme-treated starch, agar and α-cyclodextrin. Preferred are cellulose derivatives.

As described above, the organic polymer preferably is a water soluble polymer in the case the solvent is water or an aqueous organic solvent. Examples of the water-soluble polymers include carboxymethylcellulose sodium, poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic, α-starch, oxidized starch, heat-treated starch, enzyme-treated starch, and agar.

The organic polymer is preferably utilized in an amount of not less than 0.5 time, more preferably not less than 2 times as much as a weight of the benzimidazole derivative.

There is no limitation with respect to the organic solvent employed for the prepareation of a solution of the benzimidazole derivative and the organic polymer, so long as the derivative and the polymer are dissolved in the solvent. Advantageously employable are alcohols and halogenated alkyls. As described above, the organic solvent can be used in combination with water and optionally with a surface active agent.

It is not known why the benzimidazole derivatives of the formula (I) are prominently improved in the storage stability by converting a crystalline product into an amorphous product. However, it can be thought as follows.

It is observed that the benzimidazole derivative of the formula (I) emits strong heat when it decomposes. Accordingly, it is assumed that when the benzimidazole derivative in crystalline state once starts decomposition locally at a certain area, decomposition is extended rapidly to other area by way of heat produced by the strong exothermic reaction. In amorphous state, the local decomposition of the benzimidazole derivative is extended slowly to other area because the produced heat is not transmitted to the surrounding area rapidly.

It is further assumed that the organic polymer introduced into the benzimidazole derivative composition serves for forcing the formation of an amorphous compound in the conversion procedure and further serves in the composition as a barrier between the resulting amorphous particles for suppressing transmission of heat from the decomposed area to other area, whereby further improving the storage stability of the benzimidazole derivative.

According to the present invention, the improvement of storage stability of the benzimidazole derivative of the formula (I) can be accomplished by bringing the derivative into contact withand a basic material in an amount of not less than 5 weight %, preferably not less than 10 weight %, more preferably in the range of 10 to 200 weight %, based on an amount of the benzimidazole derivative. For instance, the contact between the benzimidazole derivative and the basic material can be attained by preparing a composition containing both the benzimidazole derivative and the basic material.

The basic material used herein means a material which shows pH 7 or higher, preferably pH 8 or higher, in the form of an aqueous solution or an aqueous suspension.

The basic material preferably is a hydroxide or a salt with a weak inorganic acid of a metal such as an alkali metal, an alkaline earth metal and aluminum. More concretely, the basic material preferably is a hydroxide such as alumina magnesium hydroxide ($2.5A\ell_2O_3{\bullet}Mg(OH)_2$), aluminum hydroxide and magnesium hydroxide. Examples of the salts with a weak inorganic acid include carbonates such as potassium carbonate, calcium carbonate, sodium hydrogen carbonate and magnesium carbonate; phosphates such as potassium monohydrogen phosphate, potassium phosphate and sodium phosphate; and coprecipitation products of hydroxide with carbonate such as aluminum hydroxide-sodium hydrogen carbonate coprecipitation product and aluminum hydroxide-magnesium carbonate-calcium carbonate coprecipitation product.

The basic material may be a salt of an organic acid (e.g., higher fatty acid) with an alkali metal, an alkaline earth metal, aluminum and amine. The basic material may be an amide, a basic amino acid, a thiamine and an amine. Examples of the organic acids are fatty acids having 12-22 carbon atoms, benzoic acid, alginic acid, edetic acid (EDTA), citric acid, glycyrrhizinic acid, glutamic acid, gluconic acid, succinic acid, fumaric acid, salicylic acid, and lactic acid. Preferred are higher fatty acids having 12-22 carbon atoms such as stearic acid, palmitic acid and myristic acid. Examples of the metals, include sodium, potassium, calcium, magnesium, and aluminum. Examples of the amines include isopropanolamine, diphenylamine, ethanolamine, and benzylamine.

Preferred salts of organic acids with an alkali metal, an alkaline earth metal and aluminum are sodium stearate, potassium stearate, magnesium stearate, aluminum stearate, sodium palmitate, potassium palmitate, magnesium palmitate, aluminum palmitate, sodium myristate, potassium myristate, magnesium myristate, aluminum myristate, sodium benzoate, sodium alginate, sodium edetate, sodium citrate, sodium glycirrhizinate potassium glycillycinate, sodium glutamate, sodium gluconate, potassium gluconate, sodium succinate, sodium fumarate, sodium salicyate, and calcium lactate.

Examples of the amides include nicotinic amide and monomethylnicotinic amide. An example of the basic amino acid is hystidine. An example of the thiamine is vita mine B_1. Examples of the amines include

diisopropanolamine, diphenylamine, ethanolamine and benzylamine.

In the composition containing both the benzimidazole derivative of the formula (I) and a basic material, the benzimidazole derivative preferably is present in the form of particles preferably having a mean diameter of not more than 10 µm. The benzimidazole derivative of the formula (I) is more stable when it is in the form of such fine particles.

The benzimidazole derivative can be converted into fine particles using known micronizers for the preparation of fine particles. Examples of such micronizers include mechanical micronizers such as pin mill, attrition mill, screw crusher, ring roller mill, ball mill; and hydromechanical energy micronizers such as jet mill, jet pulverizer, micronizer, reductionizer jet pulverizer and air mill.

The stabilized amorphous benzimidazole derivative and the composition of the stabilized benzimidazole derivative shows prominent inhibitory action on secretion of gastric acid and also is employable as a cytoprotective agent for gastrointestinal tract. The stabilized benzimidazole derivative of the formula (I) and the composition containing the stabilized benzimidazole derivative can be administered orally or parenterally. Examples of the preparation forms for oral administration include tablets, capsules, powder, granules, and syrup. In the formulation of these preparations, there can be used excipients, disintegrants, binders, lubricants, pigments, diluents and the like which are commonly used in the art. Examples of the excipients include glucose, sucrose, lactose, and microcrystalline cellulose. Examples of the disintegrants include starch and carboxymethylcellulose calcium. Examples of the lubricants include hardened oil and talc. Examples of the binders include hydroxypropylcellulose, gelatin and polyvinylpyrrolidone. Other additives can be also used.

The dose is generally not more than 500 mg/day, preferably about 100 µg/day to 300 mg/day, for an adult. This value is expressed in terms of the amount of the physiologically active compound, namely the benzimidazole derivative of the formula (I). The dose can be either increased or decreased depending upon the age and other conditions.

The present invention is further described by the following examples.

Synthesis of 2-(2-Dimethylaminobenzylsulfinyl)benzimidazole

(1) 2-(2-Dimethylaminobenzylthio)benzimidazole:

2-Mercaptobenzimidazole (4.73 g) was dissolved in 150 mℓ of ethanol, and to the solution was added 6.18 g of 2-dimethylaminobenzyl chloride hydrochloride. The mixture was stirred at room temperature for 30 minutes. Precipitated crystals were collected by filtration. A saturated aqueous $NaHCO_3$ solution was added to the crystals, and the resulting mixture was extracted with chloroform. The chloroform layer was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure and the residue was recrystallized from a mixture of chloroform and acetonitrile to obtain 5.39 g of 2-(2-dimethylaminobenzylthio)benzimidazole as a colorless crystalline product (m.p. 164°C).

(2) 2-(2-Dimethylaminobenzylsulfinyl)benzimidazole

2-(2-Dimethylaminobenzylthio)benzimidazole (4.8 g) was dissolved in a mixture of 40 mℓ of chloroform and 5 mℓ of methanol. After the solution was chilled to 0°C, 3.86 g of m-chloroperbenzoic acid (purity: 70%) was added portionwise. Ten minutes later, a saturated aqueous $NaHCO_3$ solution was added to the reaction mixture, and the resulting mixture was extracted with chloroform. The chloroform solution was washed with saturated brine and then dried over anhydrous sodium sulfate. The chloroform was distilled off under reduced pressure and the residue was recrystallized from a mixture of chloroform and ether to obtain 2.97 g of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole as a colorless crystalline product (m.p. 116°C, decomposed).

Example 1

In 10 ml of methyl alcohol were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole and 3.0 g of hydroxypropylcellulose. The resulting solution was placed in a rotary evaporator for concentration. The concentrated residue was poured in a Petri dish, and placed overnight in a vacuum dryer at 35°C. The dried composition product was in the form of a pale yellow film.

The composition in the form of a film was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 2

In 100 ml of chloroform were dissolved 3.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole and 9.0 g of poly(vinylpyrrolidone). The resulting solution was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 3.5 ml/min. and a temperature of supplied air at 100°C, to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 3

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 4

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 5

The procedure of Example 2 was repeated except for replacing the poly(vinylpyrrolidone) with the same amount of methylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Example 6

In 30 ml of methylene chloride were dissolved 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole and 1.0 g of a nonionic surface active agent (low HLB type) to obtain an oily solution. Independently, in 250 ml of water were dissolved 3.0 g of carboxymethylcellulose sodium and 1.0 g of a nonionic surface active agent (high HLB type) to obtain an aqueous solution.

The oily solution and the aqueous solution were combined and violently mixed to give an emulsion. The resulting emulsion was spray dried using a minispray dryer (manufactured by Yamato Kagaku Co., Ltd., Japan) at a spraying rate of 2.0 ml/min. and a temperature of supplied air at 120°C, to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. No diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in amorphous state.

Comparison Example 1

In a mortar were mixed 1.0 g of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole and 3.0 g of hydroxpropylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in crystalline state.

Comparison Example 2

The procedure of Comparison Example 1 was repeated except for replacing the hydroxypropylcellulose with the same amount of hydroxypropylmethylcellulose to obtain a fine powdery composition.

The powdery composition was analyzed by X-ray diffraction. A diffraction pattern was observed. Accordingly, it was confirmed that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole in the composition was in crystalline state.

Evaluation on Storage Stability

The 2-(2-dimethylaminobenzylsulfinyl)benzimidazole-containing compositions obtained in Examples were stored in a thermostat at 70°C for 6 days. In the course of the storage, an amount of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole remaining in the composition (i.e., remaining amount) was determined at lapse of 2 days, 4 days, and 6 days, to evaluate storage stability of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

The remaining amount of 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was determined by taking out approx. 900 mg of the stored sample, weighing the taken sample, adding methanol to the sample to make a total volume of precisely 100 mℓ under shaking for extraction by methanol, diluting the methanolic extract to make a total volume of 100 times as much as the methanolic extract, subjecting 20 μℓ of the diluted solution to determination based on HPLC (high pressure liquid chromatography) method.

The results are set forth in Table 1. The numerals in Table 1 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Table 1

Sample	Period of Storage			
	0 day	2 days	4 days	6 days
Example 1	100	98.2	96.6	86.6
Example 2	100	99.8	99.4	95.5
Example 3	100	99.5	98.8	99.2
Example 4	100	96.2	93.6	79.0
Example 5	100	95.5	90.0	85.3
Example 6	100	98.9	97.3	95.4
Com. Ex. 1	100	94.8	87.2	56.2
Com. Ex. 2	100	94.1	82.5	44.1

Examples 7 - 14

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm^2 and rate of 1 kg/hr to obtain a white microcrystallline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (decomposition point: 121-127°C, mean diameter 2 µm) in 95 % yield.

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was mixed with a basic material set forth in Table 2 at weight ratio of 1 : 1. The resulting composition was stored at 50°C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfinyl) benzimidazole was determined in the same manner described above.

The results are set forth in Table 2.

Comparison Example 3

The procedure of Example 7 was repeated except that no basic material was mixed, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

Comparison Examples 4 - 11

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 2, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The result is set forth in Table 2.

Table 2

Sample	Added Material	Remaining amount (%)
Example 7	Alumina magnesium hydroxide	88.1
Example 8	Sodium carbonate	94.7
Example 9	Calcium hydrogen phosphate	95.8
Example 10	Aluminum hydroxide	80.8
Example 11	Magnesium methasilicate aluminate	51.1
Example 12	Anhydrous calcium phosphate	97.4
Example 13	Magnesium carbonate	78.9
Example 14	Sodium hydrogen carbonate	81.2
Com. Ex. 3	-------	1.7
Com. Ex. 4	Calcium sulfate	4.1
Com. Ex. 5	Lactose	0.8
Com. Ex. 6	D-Mannitol	0.9
Com. Ex. 7	Microcrystallline cellulose	10.5
Com. Ex. 8	Corn starch	3.0
Com. Ex. 9	Polyethylene glycol	1.0
Com. Ex. 10	Methylcellulose	1.4
Com. Ex. 11	Succinic acid	0.0

Remarks: The numerals in Table 2 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 15 - 17

The procedure of Example 7 was repeated except that the basic material was replaced with that set forth in Table 3 and the storage period was changed to 30 days, to evaluate storage stability of the microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole. The results are set forth in Table 3.

Table 3

Sample	Added Material	Remaining amount (%)
Example 15	Alumina magnesium hydroxide	51.6
Example 16	Aluminum hydroxide	37.3
Example 17	Magnesium carbonate	55.0

Remarks: The numerals in Table 3 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 18 & 19 and Comparison Examples 12 - 13

The microcrylstalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole prepared in Example 7 was mixed with additives set forth in Table 4 to obtain a 2-(2-dimethylaminobenzylsulfinyl)benzimidazole-containing composition.

Table 4

	Example		Comparison
	18	19	Example 12
Benzimidazole derivative	30	30	30
Lactose	47	37	57
Corn starch	10	10	10
Alumina magnesium hydroxide	10	20	-
Hydroxypropylcellulose	3	3	3

In Table 4, the numerals are expressed in terms of weight parts.

The resulting compositions and an untreated microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (for Comparison Example 13) were kept at 50°C, 75%RH for 5 days, 10 days and 20 days, for evaluating storage stability in the same manner as described above.

The results are set forth in Table 5. The numerals in Table 5 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Table 5

Sample	Period of Storage			
	0 day	5 days	10 days	20 days
Example 18	100	99.6	95.2	93.4
Example 19	100	99.6	94.8	92.9
Com. Ex. 12	100	99.7	95.6	66.0
Com. Ex. 13	100	95.1	1.6	–

Examples 20 - 22

1.0 kg of the colorless 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was pulverized by means of a jet mill 100AS (manufactured by Fuji Sangyo Co., Ltd.) at stream pressure of 5.5 kg/cm^2 and rate of 1 kg/hr to obtain a white microcrystallline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole (decomposition point: 121-127° C, mean diameter 2 µm) in 95 % yield.

The microcrystalline 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was mixed with a basic material set forth in Table 6 at weight ratio of 1 : 1. The resulting composition was stored at 50° C, 75%RH for 16 days, and then the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was determined in the same manner described above.

The results are set forth in Table 6.

Table 6

Sample	Added Material	Remaining amount (%)
Example 20	Nicotinamide	64.6
Example 21	Magnesium stearate	63.3
Example 22	Calcium stearate	35.8

Remarks: The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylaminobenzylsulfinyl)benzimidazole.

Examples 23 & 24

The procedure of Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzyl)sulfinyl)benzimidazole (for Example 23) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Example 24) and the amount of hydroxy propyl

cellulose was changed into 5.0 g., to obtain an amorphous product. The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 and 8.

Examples 25 & 26

The procedure of Example 7 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Example 25) and 2-(2-dimethylamino-5- methylbenzylsulfinyl)benzimidazole (for Example 26). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Examples 27 & 28

The procedure of Example 21 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Example 27) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Example 28). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 14 & 15

The procedure of Comparison Example 1 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Comparison Example 14) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 15). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 16 & 17

The procedure of Comparison Example 5 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxy benzylsulfinyl)benzimidazole (for Comparison Example 16) and 2-(2-dimethylamno-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 17). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Comparison Examples 18 & 19

The procedure of Comparison Example 11 was repeated except that the 2-(2-dimethylaminobenzylsulfinyl)benzimidazole was replaced with 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole (for Comparison Example 18) and 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole (for Comparison Example 19). The test for evaluation of storage stability was performed in the same manner as described above except that the temperature and the storage period were changed to 60°C and 10 days, respectively. The results are set forth in Tables 7 & 8.

Table 7
[2-(2-dimethylamino-5-methoxybenzyl)sulfinylbenzimidazole]

Sample	Storage Period		
	0 day	5 days	10 days
Example 23	100	99.8	99.5
Example 25	100	99.2	95.9
Example 27	100	99.6	96.9
Com. Ex. 14	100	98.3	74.6
Com. Ex. 16	100	99.2	78.1
Com. Ex. 18	100	0	–
Ref. Ex. 1	100	99.4	76.3

Remarks: Sample of Ref. Ex. 1 is an untreated microcrystalline 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.
The numerals in Table 7 mean relative amounts of the remaining 2-(2-dimethylamino-5-methoxybenzylsulfinyl)benzimidazole.

Table 8

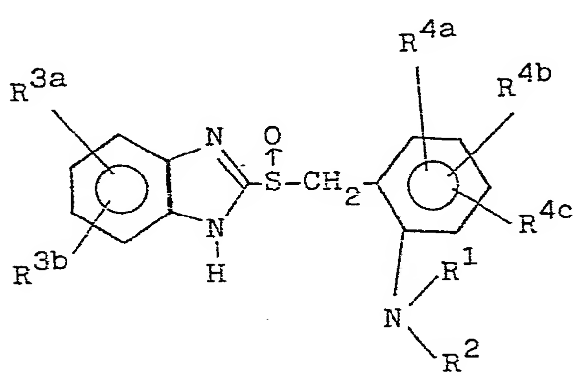
[2-(2-dimethylamino-5-methylbenzyl)sulfinylbenzimidazole]

Sample	Storage Period		
	0 day	5 days	10 days
Example 24	100	99.2	99.2
Example 26	100	75.4	49.5
Example 28	100	87.5	71.8
Com. Ex. 15	100	9.9	4.5
Com. Ex. 17	100	60.1	0.1
Com. Ex. 19	100	0	–
Ref. Ex. 2	100	30.4	10.0

Remarks: Sample of Ref. Ex. 2 is an untreated microcrystalline 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.
The numerals in Table 6 mean relative amounts of the remaining 2-(2-dimethylamino-5-methylbenzylsulfinyl)benzimidazole.

Claims

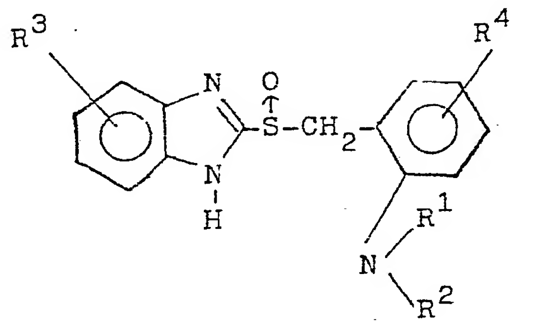
1. A physiologically active benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, which is in amorphous state.

2. The benzimidazole derivative as claimed in claim 1, wherein the benzimidazole derivative has the formula (II):



(II)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^3 and R^4 independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

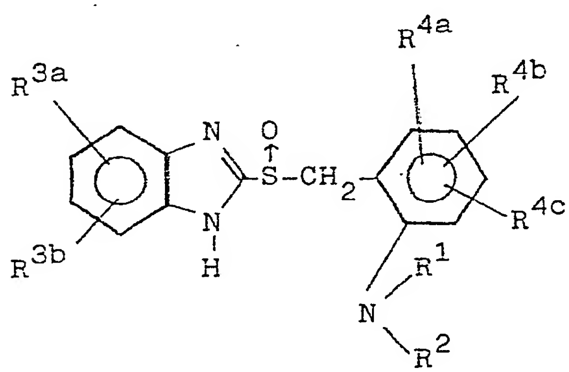
3. The benzimidazole derivative as claimed in claim 1, wherein R^1 of the formula (I) representing the benzimidazole derivative is an alkyl group containing 1 to 8 carbon atoms.

4. The benzimidazole derivative as claimed in claim 1, wherein R^2 of the formula (I) representing the benzimidazole derivative is a lower alkyl group.

5. The benzimidazole derivative as claimed in claim 1, wherein each of R^{3a} and R^{3b} of the formula (I) representing the benzimidazole derivative is hydrogen atom or a lower alkoxy group.

6. The benzimidazole derivative as claimed in claim 1, wherein each of R^{4a}, R^{4b} and R^{4c} of the formula (I) representing the benzimidazole derivative is hydrogen atom or a lower alkyl group.

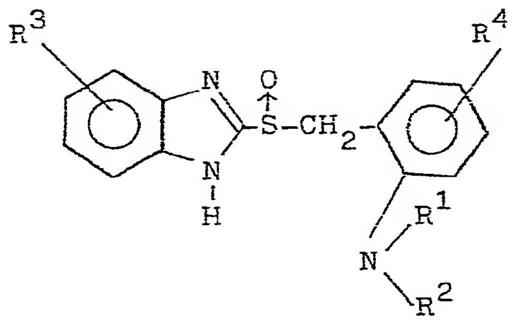
7. A composition containing a physiologically active amorphous benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, dispersed in an organic polymer.

8. The composition as claimed in claim 7, wherein the benzimidazole derivative has the formula (II):



(II)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^3 and R^4 independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

9. The composition as claimed in claim 7, wherein the organic polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, carboxymethylcellulose sodium, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(sodium acrylate), sodium alginate, gelatin, gum arabic, α-starch, oxidized starch, heat-treated starch, enzyme-treated starch and agar.

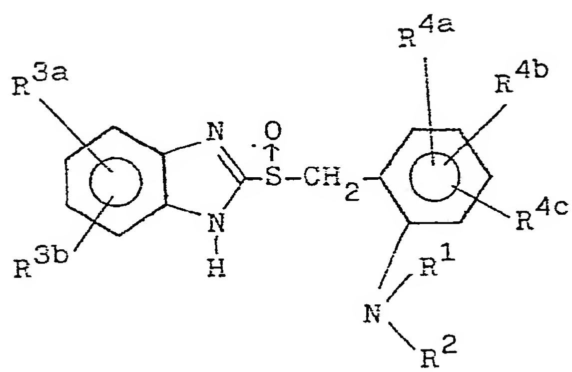
10. The composition as claimed in claim 7, wherein the organic polymer is a cellulose derivative.

11. The composition as claimed in claim 7, wherein the organic polymer is a water soluble polymer.

12. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 0.5 time as much as a weight of the benzimidazole derivative.

13. The composition as claimed in claim 7, wherein the organic polymer is contained in an amount of not less than 2 times as much as a weight of the benzimidazole derivative.

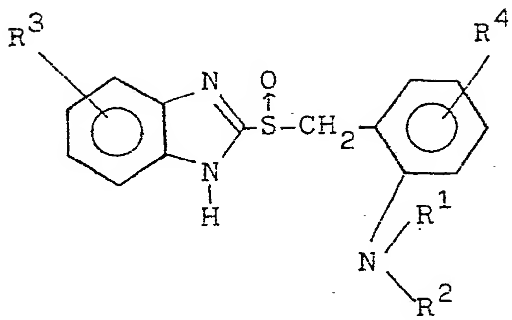
14. A composition containing a physiologically active benzimidazole derivative having the formula (I):



(I)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a fluoroalkyl group having 1 to 6 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{4c} independently is hydrogen atom, a halogen atom, a flouroalkyl group having 1 to 6 carbon atoms, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group, and a basic material in an amount of not less than 5 weight % based on an amount of the benzimidazole derivative.

15. The composition as claimed in claim 14, wherein the benzimidazole derivative has the formula (II):



(II)

wherein R^1 is hydrogen atom, an alkyl group having 1 to 8 carbon atoms, a cycloalkyl group, phenyl group or an aralkyl group, R^2 is hydrogen atom or a lower alkyl group, or R^1 and R^2 together with the adjacent nitrogen atom form a ring, and each of R^3 and R^4 independently is hydrogen atom, a halogen atom, trifluoromethyl group, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group or an amino group.

16. The composition as claimed in claim 14, wherein the basic material is a hydroxide or a salt with a weak inorganic acid of a metal selected from the group consisting of an alkali metal, an alkaline earth metal and aluminum.

17. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of alumina magnesium hydroxide, aluminum hydroxide and magnesium carbonate.

18. The composition as claimed in claim 14, wherein the basic material is a salt of an organic acid with an alkali metal, an alkaline earth metal, aluminum and amine.

19. The composition as claimed in claim 14, wherein the basic material is selected from the group consisting of amide, basic amino acids, thiamines and amines.

20. The composition as claimed in claim 14, wherein the basic material is a salt of a higher fatty acid with an alkali metal or an alkaline earth metal.

21. The composition as claimed in claim 14, wherein the basic material is contained in an amount of not less than 10 weight % based on an amount of the benzimidazole derivative.

22. The composition as claimed in claim 14, wherein the basic material is contained in an amount of 10 to 200 weight % based on an amount of the benzimidazole derivative.

23. The composition as claimed in claim 14, wherein the benzimidazole derivative is contained in the form of particles having a mean diameter of not more than 10 µm.

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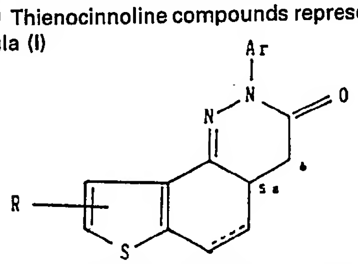
(54) **THIENOCINNOLINE COMPOUNDS AND THEIR MEDICINAL APPLICATION.**

(57) Thienocinnoline compounds represented by general formula (I)



(I)

(wherein R represents hydrogen, halogen or lower alkyl, Ar represents aryl, heteroaryl, or aryl or heteroaryl having at least one substituent selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, amino, hydroxy, trifluoromethyl and lower alkanoylamino, and ---- between 5a-position and 6-position represents either a single or a double bond) useful as anti-anxious agents, amnesia treating agents, brain function activating agents, anti-dement agents or bioprotection accelerating agents.

EP 0 308 515 A1

TITLE MODIFIED
see front page

SPECIFICATION

Thienocinnoline Compounds and their Pharmaceutical Use

[Technical Field]

This invention relates to thienocinnoline compounds which are novel and of use as pharmaceuticals and their pharmaceutical use.

[Background Art]

Benzodiazepine (BZP) derivatives represented by diazepam have been used long as an antianxiety drug or a therapeutic medicine for sleep disturbance. The recent pharmacological studies have shown that there exist receptors which exhibit a specific affinity for BZP derivatives in the central nervous system [Science, vol. 198, 849 (1977)]. In the studies and researches conducted subsequently, there have been investigated and developed not only BZP derivatives but also the compounds which have structures different from BZP but exhibit a high affinity for BZP receptors and a BZP-like action (BZP agonist), the compounds which exhibit a high affinity for BZP receptors but exhibit a pharmacological action reverse to BZP (BZP inverse-agonist) and the compounds which exhibit a high affinity for BZP receptors but nevertheless exhibit no pharmacological activity themselves and rather show an antagonistic action against the action of the agonist or the inverse-agonist (BZP antagonist) [Advance in Drug Research, vol. 14, 165 (1985)].

Since BZP derivatives which are used as an antianxiety

drug have a sedative action, a muscle-relaxing action and an anticonvulsive action in addition to an antianxiety action, they often cause troubles in terms of side effects such as dizziness and sleepiness. Thus, researches of non-BZP types of compounds aiming at developing selective antianxiety drugs with less side effects are thriving. Nevertheless, there have not been found satisfactory ones yet.

Also, in recent years, amnesia-inducing actions by BZP agonists were found [Nature, vol. 321, 864 (1986)], and there have been reports suggesting the possibility that BZP-antagonists exhibiting an antagonistic action against the amnesic actions induced by BZP agonists and BZP-inverse-agonists exhibiting an action reverse to the amnesic actions by BZP agonists are usable as brain-function activating drugs. [Trends in Neurosciences, vol. 11, 13 (1988)].

In the meantime, in the specification of U.S. Patent No. 4602019 there are disclosed compounds such as 2,4,4a,5-tetra-hydro-7-(1H-imidazol-1-yl)-3H-indeno[1,2-c]pyridazin-3-one having a cardiac action and an antihypertensive action. The Journal of Medicinal Chemistry, vol. 24, 830 (1981) discloses compounds such as 2-(4-chlorophenyl)benzothiopyrano-[4,3-c]pyrazol-3-one possessing an immune-supressing action.

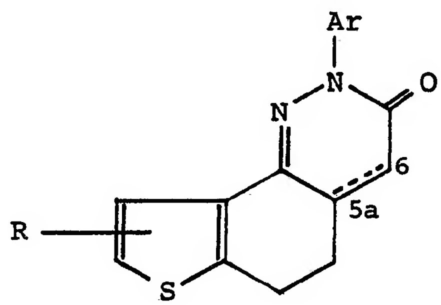
[Disclosure of Invention]

The present inventors have conducted intensive studies for the purpose of developing BZP-agonists, BZP-inverse-agonists or BZP-antagonists having a non-BZP-nucleus which

are useful pharmaceuticals and providing effective compounds and pharmaceuticals.

It has been found that the above-mentioned purpose can be attained according to the present invention described hereinafter.

That is, the first invention is to provide thienocinnoline compounds of the general formula



(I)

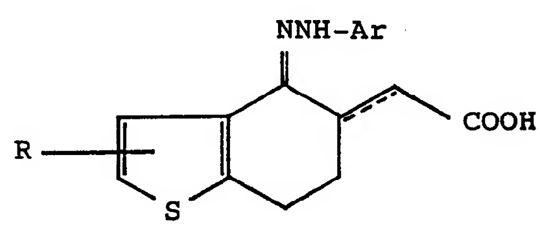
wherein R stands for hydrogen, a halogen or a lower alkyl, Ar stands for an aryl, a heteroaryl, or an aryl or a heteroaryl having as a substituent at least a halogen, a lower alkyl, a lower alkoxy, nitro, amino, hydroxy, trifluoromethyl and/or a lower alkanoylamino; and the bond ===== between 5a-position and 6-position represents a single bond or a double bond.

The second invention is to provide pharmaceutical compositions comprising a thienocinnoline compound of the above general formula (I).

The symbols of the general formùla (I) and each of the below-mentioned general formulae are defined in detail below. The halogen represents chlorine, bromine, fluorine or the like; the lower alkyl represents an alkyl having 1 to 4

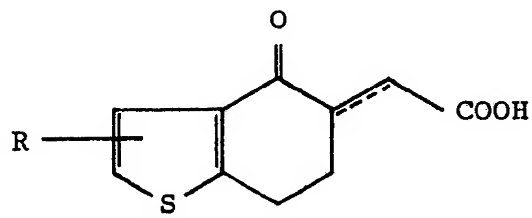
carbon atom(s) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tert-butyl; the lower alkoxy represents an alkoxy having 1 to 4 carbon atom(s) such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy or tert-butoxy; the lower alkanoylamino represents an alkanoylamino having 2 to 5 carbon atoms such as acetylamino, propionyl-amino, butyrylamino or pivaloylamino; the aryl represents phenyl, naphthyl or the like; and the heteroaryl represents a 5- or 6-membered ring or its fused ring containing 1 to 3 (preferably 1 or 2) hetero atom(s) (e.g. nitrogen, oxygen, sulfur) on the ring such as 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 3- or 4-pyrazolyl, 1- or 2-imidazolyl, 2-, 4- or 5-pyrimidinyl, 3-, 4- or 5-pyridazinyl or 2-, 4- or 5-benz-imidazolyl.

The compounds of the general formula (I) can be produced by subjecting to ring-closure reaction a compound of the formula



(IV)

wherein each of the symbols is as defined above, which can be obtained by reacting a compound of the general formula



(II)

wherein R is as defined above, with a hydrazine derivative of the general formula

$$Ar - NHNH_2 \qquad (III)$$

wherein Ar is defined as above or its acid addition salt.

The reactions proceed by heating under reflux in a suitable solvent, for example, an alcohol solvent such as methanol, ethanol or propanol for 5 to 20 hours to yield the compound of the formula (I) and the compound of the formula (IV).

In case where an acid addition salt of the hydrazine derivative of the general formula (III) is employed, the reaction is conducted in the presence of an acid scavenger (sodium acetate, potassium acetate, sodium bicarbonate, sodium carbonate, potassium carbonate, pyridine, triethylamine, etc.).

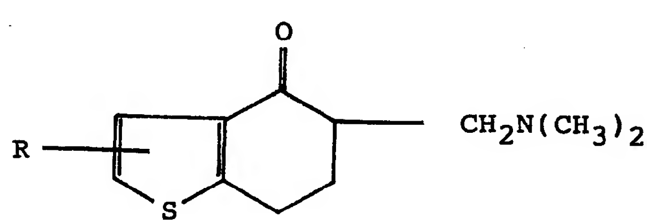
When the compound of the general formula (IV) is obtained in the above reaction, the compound of the general formula (I) can be produced by heating the obtained compound of the general formula (IV) under reflux in acetic acid for 5 - 10 hours.

The compound of the general formula (I) wherein the bond

between 5a-position and 6-position is a double bond can be synthesized also by adding bromine in an amount of 1 - 1.5 times mol dropwise to the corresponding compound of the general formula (I) wherein the bond between 5a-position and 6-position is a single bond in acetic acid as the solvent at 20 - 60°C [Journal of Medicinal Chemistry, vol. 14, 262 (1971)] or by reacting the compound of the general formula (I) wherein the bond between 5a-position and 6-position is a single bond with sodium-m-nitrobenzenesulfonate (Bachmann method, The specification of United Kingdom Patent No. 1168291).

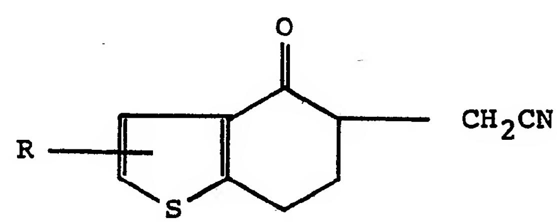
The compounds of the general formula (I) which can be produced in the above-mentioned manner can be isolated and purified by a conventional method such as column chromatography or recrystallization.

The compounds of the general formula (II) of this invention are novel compounds which have not been described in any literature. The compounds can be produced by, for example, converting the corresponding compounds of the general formula



(V)

wherein R is as defined above, or their acid addition salts to their quaternary ammonium compounds by adding methyl iodide to the compounds of the general formula (V) or their acid addition salts in acetone and retaining the mixture at room temperature for 2 - 5 hours, followed by converting the quaternary ammonium compounds to the corresponding cyano compounds of the general formula



(VI)

wherein R is as defined above, by adding potassium cyanide or sodium cyanide to the quaternary ammonium compounds in an aqueous methanol and reacting the mixture at 30 - 50°C for 4 - 10 hours, followed by adding the thus-obtained compounds of the general formula (VI) to acetic acid and conc. hydrochloric acid and heating under reflux the mixture for 5 - 12 hours.

For reference's sake, representative examples of the compounds of the general formula (II) are indicated with their physical constant below.

4-Oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid, m.p. 118 - 120°C

2-Bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid, m.p. 134 - 136°C

2-Methyl-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid, m.p. 117 - 122°C

The preparation of some of the esters of the compounds of the general formula (II) are reported by S. Kukolja et al. in Journal of Medicinal Chemistry, vol. 28, 1986 (1985).

The compounds of the general formula (I) exhibit a high affinity of 10^{-7} - 10^{-9} M to BZP receptors and have an antagonistic action against chemical convulsants such as bicuculline and pentylenetetrazole. They also exhibit an inhibitory action against amnesia induced by electro-convulsive shock.

Furthermore, they exhibit pharmacological actions such as potentiating actions of leukocyte phagocytosis, potentiating actions of macrophage-phagocytosis and protective actions against infection.

The pharmacological actions of the compounds of the present invention are shown with the experimental methods therefor below.

Experimental Example 1 : Displacement ability for Benzodiazepine

The experiment for specific affinity to benzodiazepine receptors was carried out in accordance with the method described in Life Science, vol. 20, 2101 (1977).

The crude cynaptosome fraction was isolated from the cerebral cortex of male Wistar rats aged 9 - 10 weeks, and was suspended in 50 mM Tris-hydrochloric acid buffer solution

(pH 7.4) containing 120 mM sodium chloride and 5 mM potassium chloride. These suspensions were used for the experiment.

The test compounds in several different concentrations and tritiated diazepam (in final concentration of 2 nM) were added to the synaptosome suspensions, and the mixtures were incubated at 0°C for 20 minutes. These suspensions were filtered with Whatman GF/B glassfiber filters. After the filters were washed with the above-mentioned buffer solution, the radioactivity left on the filters was measured with the use of a liquid scintillation counter.

Specific binding was determined by subtracting binding in the presence of 10^{-6} M unlabelled diazepam from total binding.

According to the foregoing experimental method, the binding force to benzodiazepine receptors of the compound of the present invention is evaluated from its displacement ability for tritiated diazepam at its binding site, which is represented by Ki value (nM).

The results of the experiment are shown in Table 1.

Table 1

Test compound (Example No.)	Affinity to BZP Receptors, Ki (nM)
3	280
4	30
5	18
6	12

7	60
9	12
10	7
11	4.5
14	5.1
24	10

Experimental Example 2 : Anti-Bicuculline Action

The anti-bicuculline action test was carried out in accordance with the method described in Life Science, vol. 21, 1779 (1977).

Male ddY mice weighing 20 - 28 g, 7 - 14 animals per group, were used. One hour after the oral administration of the test compounds, (+) bicuculline was intravenously administered at the dosage of 0.6 mg/kg, and 50% effective concentration (ED_{50}) was estimated by examining whether the tonic convulsion within 5 minutes was caused or not. The result was that the ED_{50} values of the compounds of Example 6, 10 and 24 were 50 - 100 mg.

Experimental Example 3 : Action on Experimental Amnesia

The experiment was carried out in accordance with the method described by Sara in Psychopharmacologia, vol. 36, 59 (1974).

Male ddY mice weighing 23 - 26 g, 20 animals per group, were used, and a step-through passive avoidance reflex practicing box consisting of illuminated chamber and dark chamber was used as the experimental apparatus. As the

acquisition trial of passive avoidance reflex, the animals were placed in the illuminated chamber and then allowed to enter the dark one. As soon as the animals entered the dark chamber, footshock was applied to the mouse. Experimental amnesia was caused by applying electroconvulsive shock [ECS] soon after the acquisition trial. As the experimental trial, the animals were placed in the illuminated chamber three hours after the acquisition trial, and the time which the animals took to enter the dark chamber (latency) was measured until 600 seconds. The test compounds were administered intraperitoneally (i.p.) immediately after the application of ECS.

For the evaluation of the effects, antagonistic actions against the reduction in latency, caused by the application of ESC were examined. Measured was the minimum effective dose (MED) at which a significant antagonistic action was exhibited in the mouse treated with the test compounds as compared with controls. The results are summarized in Table 2.

Table 2

Test compound (Example No.)	Anti-amnesia Action MED (mg/kg, ip)
3	0.1
4	0.5
5	0.25
7	<0.5

9	0.5
14	0.25

Experimental Example 4 : Action on Leukocyte-phagocytosis

The experiment was performed in accordance with the method by Stossel et al. [Journal of Clinical Investigation, vol. 51, 615 (1972)].

ICR mice weighing 30 - 35 g were intraperitoneally administered with glycogen. Three hours later, the leukocytes in the abdominal cavity were collected. A leukocyte suspension of 5 x 10^6 cells/ml was prepared and 200 µl of the test compound was added to the cell suspension, followed by further addition of 100 µl of mouse serum and 100 µl of dead yeast (1 x 10^8 particles/ml) thereto. The mixture was incubated at 37°C for 20 minutes. By observing more than 200 leukocytes in the reaction mixture under a microscope (400 magnifications), the number of the leukocytes which had phagocytosed at least one dead yeast was counted. The ratio of the number of phagocytic leukocytes treated with 0.1 µM of the test compounds relative to that of phagocytic leukocytes of controls was estimated. The potentiating actions on phagocytosis of the compounds of Examples 1 and 9 were 160% and 158% respectively.

Experimental Example 5 : Action on Macrophage-phagocytosis

Casein sodium was intraperitoneally administered to rats. Three to four days later, peritoneal macrophages

were collected. The phagocytosis was examined, and the relative ratio of phagocytic macrophages of the rat treated with 0.1 μM of the test compound was calculated in the same manner as Experimental Example 4. The potentiating actions on phagocytosis of the compounds of Example 2, 8 and 10 were 146%, 167% and 148% respectively.

Experimental Example 6 : Infection-protective Action

Cyclophosphamide was intraperitoneally administered to male ICR mice (weighing 23 - 27 g, aged 5 weeks) at the dosage of 200 mg/kg. Four days later, 1 x 10^{-8} CFU of E. coli 0-111 strain was subcutaneously inoculated into the mice (Controls). The test compounds (3 mg/kg) were orally administered to the mice for 3 days from the following day of the administration of cyclophosphamide. The survival rate of the treated mice relative to controls 7 days after the inoculation of E. coli was compared. Thus, the compounds of Examples 2, 8 and 11 exhibited significant increasing effects on survival rate.

As apparent from the foregoing various pharmacological studies including experiments, the compounds (I) of the present invention have a high affinity for BZP receptors and exhibit an antagonistic action against chemical convulsion-inducing agents such as bicuculline and pentylenetetrazole, whereas they influence to a small extent on somatic functions such as muscle-relaxing actions. Thus, they are useful as an antianxiety agent. Also, since they possess an inhibitory action on amnesia induced by electroconvulsive shock, they

are useful as an amnesia-treating drugs, brain function-activating drugs and antidementiac drugs. They are also of value as an antidote for excessive administration of or toxicosis by existent antianxiety drugs such as diazepam. Besides, in view of the fact that they have leukocyte-phagocytosis-potentiating actions, macrophage-phagocytosis-potentiating actions, infection-protective actions and other pharmacological actions, they are useful as a potentiating agent of biological protection.

When the compounds of the general formula (I) are used as pharmaceuticals, a therapeutically effective amount of the compounds and adequate pharmacologically acceptable additives such as excipient, carrier, diluent and so on are mixed to be formulated into a form such as tablets, capsules, granules, syrups, injectable solutions, suppositories, dispersible powders or the like and are administered in a form mentioned above. The dosage, for example, in the case of oral administration, is generally about 5 - 500 mg daily per adult, which is once a day or in divided doses several times a day administered.

[Example]

Below, this invention is more specifically described with working examples, which are not to be construed as limitative.

Example 1

4-Oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid

(3.7 g) and 1.9 ml of phenylhydrazine are dissolved in 50 ml of butanol. After the mixture is stirred at an outside temperature of 90 to 100°C for 3 hours, the solvent is distilled off. The residue is purified by column chromatography to give crude crystals, which are recrystallized from ethanol to afford 1.2 g of 8-phenyl-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 117 - 119°C.

Example 2

Using 4-chlorophenylhydrazine instead of phenylhydrazine as used in Example 1, the reaction and procedure conducted by the same method as that of Example 1 yield 8-(4-chlorophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 169 - 171°C.

Example 3

The reaction and procedure conducted in the same manner as that of Example 1 using 2-hydrazinopyridine in place of phenylhydrazine as used in Example 1 give 8-(2-pyridyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 135 - 136°C.

Example 4

The reaction and procedure conducted by the same method as that of Example 1 using 2-bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid instead of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 1 give 2-bromo-8-phenyl-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 131 - 133°C.

Example 5

By following the reaction and procedure conducted by the same method as that of Example 1 using 2-methyl-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid in place of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 1 give 2-methyl-8-phenyl-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one, m.p. 106 - 108°C.

Example 6

By following the reaction and procedure conducted by the same method as that of Example 1 using 2-bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid instead of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 1 and 4-chlorophenylhydrazine instead of phenylhydrazine, 2-bromo-8-(4-chlorophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 115 - 117°C is produced.

Example 7

By conducting the reaction and procedure by the same method as that of Example 1 using 2-bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid instead of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 1 and 2-hydrazinopyridine instead of phenylhydrazine as used in Example 1, 2-bromo-8-(2-pyridyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 138 - 141°C is produced.

Example 8

In 50 ml of butanol are dissolved 3.0 g of 4-oxo-

4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid and 2.5 g of 4-methylphenylhydrazine hydrochloride, whereto 1.3 g of sodium acetate is added. The mixture is heated under reflux for 2 hours. After the solvent is distilled off, water is added thereto. The mixture is extracted with chloroform, washed with water and dried over anhydrous magnesium sulfate. The solvent is distilled off. The obtained crude crystals are purified by column chromatography, and recrystallized from ethanol to yield 2.3 g of 8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 157 - 160°C.

Example 9

The reaction and procedure by the same method as that of Example 8 using 4-methoxyphenylhydrazine hydrochloride in place of 4-methylphenylhydrazine hydrochloride as used in Example 8 is conducted to afford 8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 190 - 192°C.

Example 10

By following the reaction and procedure by the same method as that of Example 8 using 2-bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid in place of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 8, 2-bromo-8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 142 - 144°C is produced.

Example 11

By following the reaction and procedure by the same

method as that of Example 8 using 2-bromo-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid instead of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 8 and 4-methoxyphenylhydrazine hydrochloride instead of 4-methylphenylhydrazine hydrochloride as used in Example 8, 2-bromo-8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one, m.p. 155 - 156°C is produced.

Example 12

By following the reaction and procedure by the same method as that of Example 8 using 2-methyl-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid instead of 4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-acetic acid as used in Example 8 and 4-chlorophenylhydrazine hydrochloride instead of 4-methylphenylhydrazine hydrochloride, 2-methyl-8-(4-chlorophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 137 - 139°C is obtained.

The following compounds can be obtained in the same manner as in the above examples.

Example 13

2-Methyl-8-(2-pyridyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 143 - 145°C.

Example 14

2-Methyl-8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one, m.p. 133 - 135°C.

Example 15

8-(4-Nitrophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-

h]cinnolin-7-one.

Example 16

8-(3-Trifluoromethylphenyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one.

Example 17

8-(4-Aminophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one.

Example 18

8-(4-Acetylaminophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one.

Example 19

8-(4-Hydroxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 268 - 269°C.

Example 20

2-Methyl-8-(3-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one.

Example 21

2-Methyl-8-(4-nitrophenyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one.

Example 22

2-Methyl-8-(4-acetylaminophenyl)-4,5,5a,6,7,8-hexahydro-thieno[2,3-h]cinnolin-7-one.

Example 23

2-Methyl-8-(4-hydroxyphenyl)-4,5,5a,6,7,8-hexahydro-thieno[2,3-h]cinnolin-7-one.

Example 24

2-Methyl-8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 120 - 122°C.

Example 25

8-(3-Methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 135 - 137°C.

Example 26

8-(2-Methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 148 - 150°C.

Example 27

8-(4,6-Dimethyl-2-pyrimidinyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 230 - 232°C.

Example 28

8-(6-Chloro-3-pyridazinyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, m.p. 263 - 264°C (decomposition).

Example 29

8-(4-Methoxy-2-pyrimidinyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one.

Example 30

In 50 ml of acetic acid is dissolved 1.6 g of 2-methyl-8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one as obtained in Example 24, and 0.2 ml of bromine is added to the solution while stirring at room temperature. The mixture is mixed at 80 - 90°C for 30 minutes. After the solvent is distilled off, the obtained crystals are purified by way of silica gel column chromatography, followed by recrystallization from isopropyl alcohol

to give 0.8 g of 2-methyl-8-(4-methylphenyl)-4,5,7,8-tetrahydrothieno[2,3-h]cinnolin-7-one, m.p. 160 - 162°C.

Example 31

Formulation Example

Tablets containing 10 mg of a compound of the general formula (I) are prepared in accordance with the following formulation.

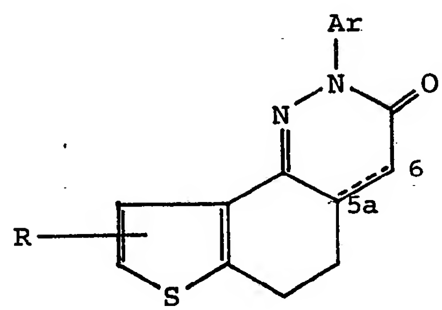
Compound of formula (I)	10.0 mg
Lactose	58.5 mg
Corn starch	25.0 mg
Crystalline cellulose	20.0 mg
Polyvinylpyrrolidone K-30	2.0 mg
Talc	4.0 mg
Magnesium stearate	0.5 mg
	120.0 mg

The compound of the formula (I) is pulverized by an atomizer into fine powders below 10 μ in average particle diameter, which are admixed with lactose, corn starch and crystalline cellulose sufficiently in a kneading machine, and further kneaded with polyvinylpyrrolidone paste. The kneaded mixture is passed through a sieve of 200 mesh, dried at 50°C and passed through a sieve of 24 mesh. Talc and magnesium stearate are mixed therewith and the mixture is compressed into 120.0 mg tablets with a punch of 8 mm in diameter. These tablets are, if desired, subjected to sugar-coating or film-coating.

While the present invention has been adequately and sufficiently described in the foregoing specification including examples, the description can be changed or modified within the spirit and scope of this invention.

Claims

1. A thienocinnoline compound of the general formula



wherein R is hydrogen, a halogen or a lower alkyl, Ar is an aryl, a heteroaryl, or an aryl or a heteroaryl which has as a substituent at least a halogen, a lower alkyl, a lower alkoxy, nitro, amino, hydroxy, trifluoromethyl and/or a lower alkanoylamino; and the bond ----- between 5a-position and 6-position is a single bond or a double bond.

2. A compound as claimed in Claim 1 which is selected from a group consisting of 8-(2-pyridyl)-4,5,5a,6,7,8-hexahydro-thieno[2,3-h]cinnolin-7-one, 2-bromo-8-phenyl-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, 2-methyl-8-phenyl-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, 2-bromo-8-(4-chlorophenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, 2-bromo-8-(2-pyridyl)-4,5,5a,6,7,8-hexahydrothieno-[2,3-h]cinnolin-7-one, 8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexa-hydrothieno[2,3-h]cinnolin-7-one, 2-bromo-8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one, 2-bromo-8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-

7-one, 2-methyl-8-(4-methoxyphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one and 2-methyl-8-(4-methylphenyl)-4,5,5a,6,7,8-hexahydrothieno[2,3-h]cinnolin-7-one.

3. A pharmaceutical composition comprising a compound as claimed in Claim 1 or Claim 2 and pharmaceutical additives.

4. An antianxiety drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

5. An amnesia-treating drug, a brain function-activating drug or an antidementiac drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

6. A potentiating agent of biological protection comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP88/00290

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl^4 C07D495/04//A61K31/495

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D495/04, A61K31/495

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	JP, B1, 57-45754 (Yoshitomi Pharmaceutical Industries, Ltd.) 29 September 1982 (29. 09. 82) Page 1, right column, lines 15 to 31, page 2, right column, lines 34 to 41 (Family: none)	1-2
Y	JP, B1, 57-45755 (Yoshitomi Pharmaceutical Industries, Ltd.) 29 September 1982 (29. 09. 82) Page 2, left column, lines 15 to 32, page 3, left column, lines 18 to 26 (Family: none)	1-2
Y	JP, A, 61-56169 (Yoshitomi Pharmaceutical Industries, Ltd.) 20 March 1986 (20. 03. 86) Claim, page 3, lines 26 to 32 & GB, A, 2185977	1-2

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

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(54) A novel pharmaceutical composition comprising exifone and water-soluble polymer.

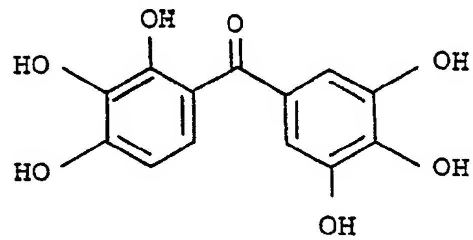
(57) A pharmaceutical composition comprising exifone and a water-soluble polymer and a process for preparing it.

EP 0 315 964 A1

A NOVEL PHARMACEUTICAL COMPOSITION COMPRISING EXIFONE AND WATER-SOLUBLE POLYMER

The present invention relates to a novel pharmaceutical composition comprising exifone and a water-soluble polymer, which improves low absorbability of exifone upon oral administration, and so is useful in the pharmaceutical field.

Exifone, which has the structure shown below, is useful as a cerebral metabolic improving agent and effective, for example, in the treatment of senile dementia, cerebrovascular dementia and the like.



[2,3,4,3′,4′,5′-Hexahydroxybenzophenone]

However, exifone is sparingly soluble in water (saturated solubility : about 70-80 μg/ml) and has disadvantage that when it is orally administered as a conventional pharmaceutical composition, its absorption into blood circulation is poor and accordingly its bioavailability is low. Therefore, the advent of a novel pharmaceutical composition which can overcome this drawback has been awaited.

The inventors of the present invention found that the above drawback can be overcome by compounding exifone and a water-soluble polymer, and as a result of our intensive investigations, we have completed the present invention.

The present invention is the first that has overcome the above drawback of exifone.

The novel pharmaceutical composition of the present invention is characterized in that it comprises exifone and a water-soluble polymer. By the coexistence of exifone and a water-soluble polymer the drawback that exifone is sparingly soluble in water is improved and high bioavailability can be attained upon oral administration.

The pharmaceutical composition of the present invention may further contain, if necessary, conventional additive(s) used ordinarily in the process of making up pharmaceutical compositions, such as disintegrants, lubricants, excipients, colorants, and so forth. The dosage form is not critical, thus, upon oral administration, the composition can be used, as desired, in the form of powders, fine granules, granules, capsules, tablets, film-coated tablets and so forth.

Suitable examples of the water-soluble polymer to be used in this pharmaceutical composition may include those ordinarily used in this field of the art, such as, for example, cellulose derivatives (e.g. hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, etc.), synthetic water-soluble polymer (e.g. polyvinylpyrrolidone, etc.) and the like. Among these, the more preferred one may be cellulose derivatives and the most preferred one may be hydroxypropylmethylcellulose and hydroxypropylcellulose.

Suitable disintegrants may include, for example, starch species (e.g. potato starch, corn starch, hydroxypropylstarch, carboxymethylstarch sodium, etc.), cellulose derivatives (e.g. carboxymethylcellulose calcium, carboxymethylcellulose, low substituted hydroxypropylcellulose, etc.) and the like. Suitable lubricants may include, for example, talc, wax species (e.g. white beeswax, hardened oils, etc.), stearic acid species (e.g. stearic acid, magnesium stearate, calcium stearate, etc.) and the like. Suitable excipients may include, for example, sugars (e.g. lactose, sucrose, etc.), starch species (e.g. corn starch, etc.), cellulose derivatives (e.g. microcrystalline cellulose, etc.), inorganic calcium salts (e.g. calcium hydrogen phosphate, calcium sulfate, etc.) and the like and suitable colorants may include, for example, tar dyes and the like. The additives are not limited to the examples mentioned above, but any additives conventionally used in this field of the art may be used.

The pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer can be produced by compounding exifone and the above-mentioned water-soluble polymer, if necessary, together with the above-mentioned conventional additive(s), and then converting the mixture to a desired dosage form.

The process for the preparation of the pharmaceutical composition of the present invention by

compounding exifone and water-soluble polymer, etc. may include the process to convert these substances to a solid dispersion composition and the process to mix these substances, and both processes are described in detail hereinbelow.

Process to convert the substances to a solid dispersion composition

The pharmaceutical composition of the present invention can be produced by converting exifone to a solid dispersion composition.

In order to convert exifone and a water-soluble polymer, if necessary, together with a conventional additive(s) to a solid dispersion composition, any procedure conventionally used in this field of the art may be used.

Thus, for instance, said composition can be produced by dissolving exifone in an appropriate organic solvent (e.g. ethanol), then adding to and dissolving or uniformly dispersing in this solution the water-soluble polymer, and after that evaporating the solvent and drying by a conventional method. When the water-soluble polymer is not satisfactorily dissolved in a solvent upon its addition thereto, another organic solvent (e.g. methylene chloride) may be added so as to dissolve it. The solvent may be selected depending upon the kind of the water-soluble polymer employed.

When above-mentioned conventional additive(s) are compounded, they may be incorporated into the composition simultaneously as the water-soluble polymer is dispersed in the composition. Alternatively, after preparation of a solid dispersion composition composed of exifone and a water-soluble polymer, said additive(s) may be compounded with said solid dispersion composition.

The thus-obtained solid dispersion composition comprising exifone and a water-soluble polymer can be converted to various dosage forms by steps conventionally used in this field of the art, for example, milling sieving, kneading, granulating, tableting, coating, etc. These steps may be carried out in the conventional manner.

Process to mix the substances

The pharmaceutical composition of the present invention can be produced by mixing exifone with a water-soluble polymer, if necessary, together with a conventional additive(s).

The means of mixing to be used in this process may be any means conventionally employed in this field of the art. For further decreasing the particle size, the resulting mixture may be milled. The milling can be performed by a conventional method.

The thus-produced mixture comprising exifone and a water-soluble polymer, etc., if desired, can be converted to various dosage forms by the steps mentioned above for the Process to convert the substances to a solid dispersion composition.

This process, Process to mix the substances, is suitable for industrial production because of its being easy to perform.

In producing the pharmaceutical composition of the present invention by this process, it is particularly preferable to knead the mixed powder with a suitable kneading solvent and then convert the kneaded matter to the desired dosage form. Suitable kneading solvents may include water, ethanol, and mixtures thereof.

The pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer can be produced by the above-mentioned processes. In its production, the kind and the amount of the water-soluble polymer and additive(s) to be used can be selected suitable depending, for example, upon the desired dosage form, the content of exifone therein, the desired dissolution pattern of exifone, and so forth.

When the water-soluble polymer to be used is a cellulose derivative, for instance, the compounding ratio of exifone and the water-soluble polymer is preferably about 1:0.01 to about 1:7 by weight, more preferably 1:0.05 to 1:5 by weight.

When a water-soluble polymer of another kind is used, it is possible for those skilled in the art to determine an appropriate compounding ratio with ease by studying the dissolution pattern, etc. of the composition.

In the following, the present invention is explained in detail by Examples.

[I] Process to convert the substances to a solid dispersion composition.

Example 1

Exifone (10 g) was dissolved in ethanol (150 ml). To this solution was added TC-5R (5 g) (trademark, product of Shin-Etsu Chemical; generic name; hydroxypropylmethylcellulose), and the mixture was stirred for achieving dispersion. Furthermore, methylene chloride (50 ml) was added to dissolve TC-5R completely, and after that, the solvent was evaporated.

The residue was dried overnight in vacuo at room temperature, and then milled and sieved (20 mesh) to give a solid dispersion composition.

Example 2

A solid dispersion composition was produced from exifone (10 g) and TC-5R (2 g) according to a similar manner to that of Example 1.

Example 3

A solid dispersion composition was produced from exifone (10 g) and TC-5R (10 g) according to a similar manner to that of Example 1.

Example 4

A solid dispersion composition was produced from exifone (10 g) and TC-5R (30 g) according to a similar manner to that of Example 1.

Example 5

A solid dispersion composition was produced from exifone (10 g) and TC-5R (50 g) according to a similar manner to that of Example 1.

Example 6

Exifone (10 g) was dissolved in ethanol (150 ml), then TC-5R (5 g) was added to and dispersed in this solution, and methylene chloride (50 ml) was added for complete dissolution of TC-5R. To the solution obtained was added and therein dispersed Explotab (2.5 g) (trademark; product of Kimura Sangyo; generic name : carboxymethylstarch sodium). The solvent was evaporated, and the residue was dried overnight in vacuo at room temperature, then milled and sieved (20 mesh) to give a solid dispersion composition.

[II] Process to mix the substances

Example 7

Exifone (10 g) was placed, together with TC-5R (5 g) and Explotab (2.5 g), in a polyethylene bag, and the contents were mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 8

Exifone (10 g) and TC-5R (5 g) were placed in a polyethylene bag, and the contents were mixed by shaking it well, then the mixture was milled in a coffee mill for 5 minutes. Explotab (2.5 g) was added to the milled mixture, and the whole was placed in a polyethylene bag and mixed by shaking it well to give a mixed powder comprising TC-5R-treated exifone.

Example 9

After exifone (10 g) and TC-5R (0.5 g) were mixed together in a beaker, the resulting mixture was then kneaded with a 20% aqueous ethanol solution (4 ml) and granulated. After dried in vacuo, the granules were milled in a mortar to an appropriate size and filled into No. 0 capsules to give a capsulated composition.

The formulation per one capsule was as follows :

Exifone	200 mg
TC-5R	10 mg
	210 mg

Example 10

A capsulated composition having the following formulation was produced from exifone (10 g) and HPC-L (0.5 g) (trademark; product of Nippon Soda; generic name : hydroxypropylcellulose) according to a similar manner to that of Example 9 :

Exifone	200 mg
HPC-L	10 mg
	210 mg

Example 11

Exifone (10 g) was mixed with TC-5R (1.5 g) in a beaker, and then the mixture was kneaded with a 20% aqueous ethanol solution (5 ml) and granulated. After dried in vacuo, the granules were milled in a mortar and then placed with Explotab (0.35 g) in a polyethylene bag and the mixture was mixed by shaking the bag well to give a TC-5R-treated powder. This mixed powder was filled into No. 0 capsules to give a capsulated composition, each capsule having the following formulation :

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
	237 mg

Example 12

To the mixed powder comprising TC-5R-treated exifone as obtained according to a similar manner to that of Example 11 was added magnesium stearate (0.15 g) and tabletted by a single punch tabletting machine to give tablets, each having the following formulation :

Exifone	200 mg
TC-5R	30 mg
Explotab	7 mg
Magnesium stearate	3 mg
	240 mg

Example 13

A capsulated composition was produced from exifone (10 g) and TC-5R (2.5 g} according to a similar manner to that of Example 9, each capsule having the following formulation :

Exifone	200 mg
TC-5R	50 mg
	250 mg

Example 14

A capsulated composition was produced from exifone (10g), TC-5R (2.5 g) and Explotab (2.5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

Exifone	200 mg
TC-5R	50 mg
Explotab	50 mg
	300 mg

Example 15

A capsulated composition was produced from exifone (10g), TC-5R (5 g) and Explotab (2.5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

Exifone	200 mg
TC-5R	100 mg
Explotab	50 mg
	350 mg

Example 16

A capsulated composition was produced from exifone (10g), TC-5R (10 g) and Explotab (5 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

Exifone TC-5R Explotab	100 mg 100 mg 50 mg
	250 mg

Example 17

A capsulated composition was produced from exifone (10 g), TC-5R (30 g) and Explotab (20 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

Exifone TC-5R Explotab	50 mg 150 mg 100 mg
	300 mg

Example 18

A capsulated composition was produced from exifone (10 g), TC-5R(50 g) and Explotab (20 g) according to a similar manner to that of Example 11, each capsule having the following formulation :

Exifone TC-5R Explotab	50 mg 250 mg 100 mg
	400 mg

Example 19

Exifone (200 g) and TC-5R (100 g) were mixed with each other by shaking well in a polyethylene bag, the mixture was then kneaded with a 20% aqueous ethanol solution(80 ml) as a kneading solvent and granulated using a Planetary mixer for kneading. The granules obtained were dried at 40° C in vacuo and then milled using Tornado type mill (20 mesh). The powder obtained was mixed with Explotab (27 g) in a polyethylene bag, and the resulting mixture was filled into No. 0 capsules to give a capsulated composition, each having the following formulation :

Exifone TC-5R Explotab	200 mg 100 mg 27 mg
	327 mg

Example 20

(1) To the TC-5R-treated powder (before filling into capsules) obtained in Example 19 was added Explotab, Avicel (trademark; product of Asahi Chemical Industry; generic name : microcrystallinecellulose) and magnesium stearate, and then the mixture was tableted in the conventional manner to give tablets each having the following formulation :

Exifone	200 mg
TC-5R	100 mg
Explotab	37 mg
Avicel	20 mg
Magnesium stearate	3 mg
	360 mg

(2) The above tablets were film-coated by a conventional method to give film-coated tablets. The formulation of film coat layer per tablet was as follows :

TC-5R	5.4 mg
Polyethylene glycol 6000	0.8 mg
Titanium oxide	1.7 mg
Yellow iron sesquioxide	0.1 mg
	8.0 mg

Example 21

Exifone (750 g), TC-5R (375 g), Explotab (101.25 g), lactose (678.75 g) and avicel (678.75 g) were mixed, granulated with an aqueous solution of citric acid (18.75 g), dried and sieved in a conventional method to give granules (2540 g). The granules obtained were mixed with magnesium stearate (33.08 g) and then tabletted in a conventional manner. The tablets thus obtained were film-coated in a conventional method to give film-coated tablets, each having the following formulation :

Core Tablet	
Exifone	40 mg
TC-5R	20 mg
Explotab	5.4 mg
citric acid	1 mg
lactose	35.6 mg
Avicel	36.2 mg
magnesium stearate	1.8 mg
	140 mg

Film Coat Layer	
TC-5R	3.8 mg
Polyethylene glycol 6000	0.5 mg
titanium oxide	0.56 mg
yellow ferric oxide	0.14 mg
carnauba wax	trace
	5 mg

In the pharmaceutical composition of the present invention the solubility of exifone was markedly

improved as compared with the exifone bulk substance and, when orally administered, a sufficient bioavailability can be obtained.

In the following, for demonstrating the above fact, we set forth the dissolution test results and absorption test results (in dogs) obtained with several representative pharmaceutical compositions produced in accordance with the present invention.

Dissolution test 1

[I] Compositions tested

Composition A :	The solid dispersion composition obtained in Example 1 (exifone : TC-5R = 1:0.5)
Composition B :	The solid dispersion composition obtained in Example 4 (exifone : TC-5R = 1:3)
Control composition :	Exifone bulk substance (200 mg) filled in a No. 0 capsule

[II] Test method

The dissolution percent was determined with passage of the time by the dissolution test method (2nd method) prescribed in the 11th edition of The Pharmacopoeia of Japan. The test conditions were as follows :

Dissolution tester :	Toyama Sangyo model
Sample quantity :	200 mg as exifone
Test solution and its quantity :	1st fluid (pH 1.2), 900 ml
Paddle speed :	100 rpm
Measurement :	uv wavelength 385 nm

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

Time (minutes) / Test composition	30	60
Composition A	77.0	89.0
Composition B	33.0	48.0
Control composition	11.4	12.4

The above test results clearly shows that in the pharmaceutical composition of the present invention produced by the process to convert the substances to a solid dispersion composition their dissolution patterns were markedly improved as compared with the exifone bulk substance. The drawback of exifone, its sparing solubility, has thus been markedly improved.

Dissolution test 2

[I] Compostion tested

Composition C :	The mixed powder comprising TC-5R-treated exifone obtained in Example 7 (exifone : TC-5R = 1:0,5)
Composition D :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 9 (exifone : TC-5R = 1:0.05)
Composition E :	The capsule containing a mixed powder comprising HPC-L-treated exifone obtained in Example 10 (exifone:HPC-L = 1:0.05)
Composition F :	The tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 12 (exifone : TC-5R = 1:0.15)
Composition G :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 13 (exifone : TC-5R = 1:0.25)
Composition H :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 15 (exifone : TC-5R = 1:0.5)
Control composition :	The same control composition as used in Dissolution test 1.

[II] Test method

The same method as used in Dissolution test 1 was used.

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

Test composition \ Time (minutes)	30	60
Composition C	52.1	68.1
Composition D	78.4	83.1
Composition E	68.3	71.7
Composition F	85.8	88.6
Composition G	80.2	93.8
Composition H	81.6	84.9
Control composition	11.4	12.4

The above test results show that in the pharmaceutical compositions of the present invention as produced by the process to mix the substances, whether in the form of mere mixtures or in any of the various dosage forms derived therefrom and in any of the varied mixing ratios, their dissolution patterns were markedly improved as compared with the exifone bulk substance and that, therefore, the drawback of exifone, its sparing solubility, has been markedly improved.

Since it has been so far believed that mere mixing of a sparingly soluble medicinal substance with a water-soluble polymer can hardly be expected to result in an improved solubility, the finding that mere mixing may produce a marked improvement as in the pharmaceutical composition of the present invention may be said to be a quite unexpected one.

Dissolution test 3

[I] Compositions tested

Composition I :	The solid dispersion composition obtained in Example 6 filled in No. 0 capsules in an amount of 200 mg as exifone per capsule (exifone : TC-5R = 1:0.5)
Composition J :	The capsule containing a mixed powder comprising TC-5R-treated exifone obtained in Example 19 (exifone : TC-5R = 1:0.5)
Composition K :	The film-coated tablet comprising a mixed powder comprising TC-5R-treated exifone obtained in Example 21 (exifone : TC-5R = 1:0.5)
Control composition :	The same control composition as used in Dissolution test 1.

[II] Test method

The same method as used in Dissolution test 1 was used

[III] Test results

The dissolution percent obtained at each measurement time was as follows :

Test composition \ Time (minutes)	5	15	30	60	120
Composition I	22.9	64.0	77.5	83.5	87.5
Composition J	33.1	60.5	70.8	72.9	81.7
Composition K	13.4	61.8	74.5	79.1	79.1
Control composition	10.4	10.5	11.4	12.4	16.0

For demonstrating that an improvement in dissolution behavior can lead to an improvement in absorption upon oral administration, an absorption tests were performed in dogs using the representative pharmaceutical compositions of the present invention. The results are shown below.

Absorption test 1

[I] Compositions tested

Composition I, Composition J and Control composition, as used in Dissolution test 3 were used.

[II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the three-way cross-over method.

The dose was 200 mg as exifone per dog (1 capsule of each test composition) and the test compositions were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}), times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-6}) are shown in the following table. Each data is given in terms of "mean ± standard error".

Test composition \ Time	Plasma concentration (μg/ml)						
	15 min	30 min	60 min	120 min	180 min	240 min	360 min
Composition I	1.12 ±0.56	2.12 ±0.55	1.08 ±0.18	0.39 ±0.04	0.22 ±0.07	0.15 ±0.07	0.13 ±0.06
Composition J	0.99 ±0.45	1.28 ±0.22	0.96 ±0.13	0.54 ±0.12	0.19 ±0.06	0.18 ±0.06	0.15 ±0.07
Control composition	0.07 ±0.05	0.15 ±0.07	0.14 ±0.06	0.20 ±0.07	0.11 ±0.07	0.07 ±0.07	0.10 ±0.10

Test compound	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-6} (μg•hr/ml)
Composition I	2.18	0.60	2.86
	±0.55	±0.10	±0.20
Composition J	1.50	0.50	2.59
	±0.36	±0.11	±0.41
Control composition	0.30	1.58	0.69
	±0.06	±0.58	±0.17

Absorption test 2

[I] Compositions tested

Composition J and Composition K as used in Dissolution test 3 were used.

[II] Test method

The absorption test was performed in six male beagle dogs (weighing 9.0-11.5 kg; fasted from the previous day) by the two-way cross-over method.

The dose was 200 mg as exifone per dog (1 capsule of Composition J and 5 tablets of Composition K) and the test composition were administered orally. After administration, blood samples were taken from the antebrachial vein with passage of the time and immediately assayed for exifone by the HPLC method.

[III] Test results

Plasma concentrations at each measurement time after oral administration, maximum plasma concentrations (C_{max}), times required for the plasma concentration to reach a maximum (T_{max}), and areas under the plasma concentration-time curve (AUC_{0-8}) are shown in the following table. Each data is given in terms of "mean ± standard error".

Time / Test composition	Plasma concentration (μg/ml)							
	15 min	30 min	60 min	120 min	180 min	240 min	360 min	480 min
Composition J	0.50 ±0.75	1.20 ±0.70	1.01 ±0.36	0.56 ±0.34	0.42 ±0.43	0.38 ±0.46	0.15 ±0.07	0.13 ±0.08
Composition K	0.74 ±0.84	1.47 ±0.37	0.96 ±0.06	0.47 ±0.28	0.20 ±0.05	0.16 ±0.07	0.14 ±0.04	0.13 ±0.05

Test compound	C_{max} (μg/ml)	T_{max} (hr)	AUC_{0-8} (μg•hr/ml)
Composition J	1.52 ±0.39	1.33 ±1.35	3.34 ±0.88
Composition K	1.66 ±0.34	0.50 ±0.15	2.78 ±0.42

The above test results clearly show that, as expected on the basis of the results of Dissolution test 3, in the pharmaceutical compositions of the present invention, whether obtained by the process to convert the substances to a solid dispersion composition or by the process to mix the substances, the absorbability into the blood circulation were markedly increased as compared with the exifone bulk substance.

In view of the results of the various tests mentioned above, it is apparent that, in the pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer, both the drawback of exifone, namely, its being sparingly soluble in water, and the low absorbability into blood circulation upon oral administration, which is due to the sparing solubility of exifone, have been improved to a remarkable extent, and so the pharmaceutical composition of the present invention which comprises exifone and a water-soluble polymer is very useful.

Claims

1. A pharmaceutical composition comprising exifone and a water-soluble polymer.

2. A pharmaceutical composition of claim 1, which comprises a solid dispersion composition comprising exifone and a water-soluble polymer.

3. A pharmaceutical composition of claim 1, which comprises a mixture comprising exifone and a water-soluble polymer.

4. A pharmaceutical composition of claim 2 or claim 3, wherein a water-soluble polymer is cellulose derivatives.

5. A pharmaceutical composition of any of claims 1 to 4, wherein the compounding ratio of exifone and a water-soluble polymer is about 1:0.01 to about 1:7 by weight.

6. A process for preparing a pharmaceutical composition comprising exifone and a water-soluble polymer, which comprises

i) converting exifone and a water soluble polymer to a solid dispersion composition, or

ii) mixing exifone with a water-soluble polymer.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 8627

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X,Y	FR-A-2 377 202 (LABORATORIES PHARMASCIENCE) * Page 1, lines 3-9; page 3, lines 7-16; examples 2,3; claims *	1-6	A 61 K 31/12 A 61 K 47/00
Y	FR-A-2 257 272 (LABORATORIES PHARMASCIENCE ET GAZAVE) * Claims *	1-6	
Y	EP-A-0 240 773 (FUJISAWA PHARMACEUTICAL) * Page 2, line 44 - page 3, line 40; claims *	1-6	
Y	EP-A-0 137 198 (FUJISAWA PHARMACEUTICAL) * Page 2, line 3 - page 3, line 25; claims *	1-6	
Y	DE-A-1 492 034 (MERCK AG) * Page 1, lines 1-3; page 2, line 25 - page 3, line 19; claims *	1-6	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24-01-1989	GOETZ G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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& : member of the same patent family, corresponding document

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(54) Antacid compositions with prolonged gastric residence time.

(57) Antacid powders, tablets etc. of prolonged gastric residence time have an internal phase of a solid antacid and excipient surrounded by a solid external phase containing a hydrophobic substance e.g. an ester of glycerol with palmitic or stearic acid, a hydroxylated polyalkene and a non-ionic emulsifier.

EP 0 338 861 A2

Description

ANTACID COMPOSITIONS WITH PROLONGED GASTRIC RESIDENCE TIME

This invention relates to antacid compositions having a prolonged gastric residence time.

Classical antacids such as aluminium and magnesium hydroxide gels and co-gels and the new crystalline aluminium magnesium hydroxycarbonates or sulphates such as Hydrotalcite, Almagate and Magaldrate are either rapidly neutralized to water soluble ions or sediment in the fundus of the stomach, and are evacuated into the duodenum by normal peristalsis with subsequent loss of unused drug from its site of action. Consequently they do not neutralize the continuous outout of hydrochloric acid by the parietal cells in the human stomach for a prolonged period of time.

The present invention provides solid oral pharmaceutical preparation with protracted action consisting of an internal phase of discrete solid granules containing the active antacid ingredient and a solid external phase surrounding the said granules. The internal phase consists of a powder mixture containing the active antacid ingredient and pharmaceutically acceptable excipients and the external phase contains a hydrophobic organic substance, particularly stearic, or palmitic acid esters, a hydroxylated polyalkene polymer and a non-ionic emulsifier.

The preparations described in this invention do not sediment to the fundus of the stomach, are more slowly evacuated to the duodenum by peristalsis and are available in the stomach to neutralise the hydrochloric acid secreted by the parietal cells for a prolonged period of time, and consequently resolve an important problem in the field of antacid therapy.

It is well known that hyperacidity alone does not cause ulcers, but can be a factor in their formation, and can also inhibit healing of preformed ulcers. However, it is desirable that hyperacidity be reduced and an antacid should satisfy the following criteria:

- The neutralizing effect must be rapid and maintained during normal digestion time in the stomach.
- It must neutralise the required amount of acid.
- It must raise the pH value of the gastric contents to a level at which pepsin activity is reduced but not fully inhibited.
- It should not cause the gastric pH to rise above 6.
- It should not cause systemic alkalosis even when administered repeatedly.
- The antacid should not be emptied into the duodenum until it has exerted its full effect in the stomach.

The present invention includes two-phase solid oral pharmaceutical compositions: e.g. in the form of powder, tablets (effervescent, chewable), coated tablets or capsules, with prolonged antacid activity. The composition may be prepared by granulation of a powder mixture containing the active antacid ingredient, a solid carrier and other excipients with an organic emulsion containing hydrophobic and hydrophilic components, to form granules surrounded by an external phase which, owing to its specific physico-chemical properties, prolongs the liberation of the active ingredient thereby augmenting its biological utilization. The resulting granules can then be tableted or filled into capsules. The granulating emulsion may contain as hydrophobic component, for example, esters of 12-hydroxystearic, stearic, or palmitic acid and, as hydrophilic component, a hydroxylated polyalkene polymer. By appropriate selection of the components of the emulsion, particularly the non-ionic surface active agent, e.g.polyoxyethylene sorbitan esters and changing their quantitative ratio, the rate of liberation and gastric residence time of the active ingredient can be modified.

More specifically this invention provides compositions of products with antacid properties in which the active component is a crystalline synthetic antacid such as Almagate, Hydrotalcite, Magaldrate; the compositions may also contain aluminium hydroxide or aluminium magnesium hydroxide cogels, in a vehicle which provides a prolonged gastric residence time. The prolonged residence time is a function of the lipophilicity of the particles which preferentially adhere to the gastric mucosa or form a layer on the surface of the gastric contents. The antacid is then slowly liberated, reacts with hydrogen ions in the vicinity, protects the mucosa and its emptying from the stomach is delayed in spite of peristaltic movements. The invention involves coating the particles of the antacid product with a solid emulsion of selected excipients, which increases the lipophilicity and delays reaction with hydrogen ions without altering the intrinsic acid neutralising properties.

The hydrophilic component of the emulsion can be a hydroxylated polyalkene polymer, with molecular weight 950-10.000, preferably 5000-7000, and the hydrophobic component can be glycerol mono-, di- or tripalmitic or stearic esters, or preferably hydrogenated mono-, di- or triglycerides, especially those containing 70-90% of 12-hydroxystearic acid esters and 10-30% of stearic acid esters. A non-ionic surface active agent, suitable for use with water in oil emulsions can be used as an emulsion stabiliser. The selection of the optimal composition for delaying active ingredient liberation and increasing gastric residence time may be calculated from the hydrophilic-lipophilic balance (HLB) of the components of the granulating emulsion. Non-ionic emulsifiers such as polyoxyethylene-sorbitan-monooleates, polyoxyethylene-sorbitan-monolaurates, polyoxyethylene-sorbitan-monostearates and monopalmitates, and preferably sorbitan fatty acid esters lauric, palmitic, oleic) with a hydrophilic-lipophilic balance lower than 7, generally give satisfactory results if the amount of the hydrophobic component emulsified in the granulating liquid is between 50-90 parts, preferably 80 parts by weight and the hydrophilic component is between 10-20, preferably 13 parts by weight. Such granulating emulsions are expediently prepared by dissolving the hydrophobic component in a convenient amount of chloroform or methylene chloride warming to 30

C, adding the emulsifier to the solution thus obtained, and emulsifying with the hydrophilic compound.

The resulting granulating emulsion can then be used for granulating the powder mixture containing active ingredients, carrier, and optionally other excipients. For example, one part by weight of the powder mixture is admixed and kneaded, preferably with 1.3 parts by weight of granulating emulsion. The wet mass, is kneaded again with a solution of a binder e.g. gelatin, polyvinylpyrrolidone, hydroxypropylcellulose, preferably an aqueous 3% solution of polyvinylpyrrolidone, and finally the wet mass granulated by known methods e.g. by pressing through a sieve. Flavouring substances, disintegrants and lubricating agents, such as cross-linked sodium carboxymethylcellulose and magnesium stearate, can then be added to the dried granules and the mixture pressed into tablets or filled into bottles, individual sachets or hard gelatin capsules.

The preferred pharmaceutical forms for utilization of the preparation of this invention are powders, granulates, or chewable tablets, which may or may not be combined with an adequate amount of uncoated active component to ensure a rapid initial acid neutralization. The dose of antacid (uncoated and coated) should be sufficient to neutralize the acid output of the parietal cell over a prolonged time period by limiting the loss of unused antacid by periodic gastric emptying. With conventional antacids this would only be possible with high doses of the active principles causing gastric pH to rise above 6. In addition loss of unchanged antacid by normal peristalsis into the duodenum where its presence is either not required or unwanted reduces their clinical utility.

The present invention provides:

1) The possibility of administration of higher, and more efficacious doses of antacid with longer intervals between doses.

2) Physical protection of the gastric mucosa against fluctuations of pH.

3) Prolonged antacid effect, favouring patient comfort and compliance.

4) More complete utilization of the adminstered dose by prolonged residence time in the stomach.

5) Reduction of gastro-oesophageal acid reflux due to the presence of a reserve of floating antacid on the surface of the gastric contents.

In an additional aspect of this invention the above compositions may be combined with substances which inhibit gastric acid secretion, e.g., cimetidine, ranitidine or other H_2-antihistamines or proton pump blockers for the treatment of gastrooesophageal reflux disease and gastroduodenal ulcers.

Further details of the present invention are to be found in the following Examples without limiting the scope of the claims to the Examples.

EXAMPLE 1

For the production of a granulate preparation with floating and protracted dissolution properties the following quantities of substances are used per gram of final product:

Hydrotalcite	0.75 g
Hydrophobic silicon dioxide	0.14 g
Sorbitan monooleate 60	0.005 g
Polyoxyethylene stearate	0.01 g
Castorwax	0.06 g
Polyvinylpyrrolidone	0.035 g

The hydrotalcite and hydrophobic silicon dioxide are milled to a particle diameter less than 125 microns, (very fine powder) and are mixed to form a homogeneous mixture, then kneaded successively with granulating liquids A and B prepared as follows:

Granulating liquid A:

Sorbitan monooleate, polyoxyethylene stearate, and castorwax are dissolved in warm (35 C) methylene chloride.

Granulating liquid B:

Polyvinylpyrrolidone is dissolved, with vigorous stirring in 96% by vol. ethyl alcohol, at room temperature.

The wet mass is passed through a sieve (no 14 ASTM), dried (60 C, air circulating oven), finishing and lubricating substances (e.g. magnesium stearate and Aerosil) are admixed, and the mixture is dosed into multidose plastic bottles.

Utilising the above process granulate preparations of almagate and magaldrate can be prepared containing 0.75 g of active principal per g. of granulate.

EXAMPLE 2

For the production of chewable tablets the following materials are used:

	Amount per tablet
Magaldrate	0.75 g
Silicon dioxide	0.14 g
Polysorbate 21	0.001 g
Sorbitan Monooleate 60	0.004 g
Polyethyleneglycol 400	0.02 g
Glycerine tripalmitate	0.06 g
Polyvinylpyrrolidone	0.06 g
Mannitol	0.97 g

A granulate is prepared as described in Example 1 and is then blended with an auxiliary granulate of mannitol, prepared conventionally using an aqueous solution of polyvinylpyrrolidone as granulating liquid, to improve the flow properties of the powder. The mass is lubricated with e.g magnesium stearate and tablets are produced in conventional tableting equipment.

Utilising the above process tablets containing 0.75 g of almagate or hydrotalcite can be prepared.

EXAMPLE 3

Chewable tablets containing coated and uncoated antacid are prepared using the following materials:

	Amount per tablet
Almagate (antacid)	1.5 g
Hydrophobic silicon dioxide	0.14 g
Sorbitan Monooleate 60	0.005 g
Polyethyleneglycol 6000	0.01 g
Glycerol-tris-12-hydroxystearate	0.06 g
Mannitol	1.45 g
Potato starch	0.04 g
Polyvinylpyrrolidone	0.09 g

A mixture of a portion of antacid (between 50% and 70%) is mixed with the hydrophobic silicon dioxide and granulated as described in Example 1. The remainder of the antacid (up to 30%-50% of total amount) is blended with an equal weight of mannitol, potato starch is added, and the mixture is kneaded using a 6% aqueous solution of polyvinylpyrrolidone as granulating liquid.

The two granulates are mixed with a granulate of mannitol prepared as described in Example 2, flavour and lubricating agents are added, and the product is finally pressed into chewable tablets.

Utilising the above process tablets containing 1.5 g of hydrotalcite or magaldrate can be prepared.

The long lasting antacid effect of these preparations has been demonstrated by a modification of Fordran's test (Fordtran, J.S., Morawski, S.G., Richardson, C.T., New Engl. J. Med. 288, 923 (1973)) comparing the pure antacid with the formulations using the same amount of antacid in each case.

The modification consists of delaying the time of the first addition of gastric juice until the pharmaceutical composition had spontaneously disintegrated in a volume of up to 15 ml of distilled water. At this point the addition of synthetic gastric juice was commenced.

In this test the following results were obtained:

	Pure Almagate	Tablets prepared according to Example 3
Sample Weight	1.5 g	3.295g (equivalent to 1.5 g of Almagate)
pH at 10 min (after the first addition of 150 ml gastric juice)	4.70	4.98
Time above pH 3	68 min	115 min
Volume of HCL (0.079N) consumed	520.30 ml	527.02 ml

The coated product has a longer duration of action, i.e. a 1.7 times higher than that observed with the pure antacid.

The products of this invention have an "in vitro" bioavailability similar to that of the pure antacid, (Moragues, J., Beneyto, J.E., Fabregas, J.L., Spickett, R.G.W, Arzneim. Forsch., 34 (11), 10 a, 1346 (1984)).

The floating characteristics and prolonged gastric residence time with sustained acid neutralisation have been demonstrated in human volunteer studies using isotope labelled Almagate (scintigraphy).

In normal volunteers the time required for emptying 20% of the labelled antacid from the stomach is almost 3 times longer for coated Almagate than for the uncoated product. The latter empties with the liquid phase of a light standard meal whereas emptying of the former occurs much later with a half-life of 4 hours.

Claims

1. A solid pharmaceutical preparation having an internal phase which is a powder mixture of discrete solid granules of an antacid and a pharmaceutically acceptable excipient, the internal phase being surrounded by a solid external phase containing a hydrophobic organic substance, a hydroxylated polyalkene and a non ionic emulsifier.

2. A preparation according to claim 1, wherein the antacid is Almagate, Hydrotalcite, Magaldrate or other aluminium hydroxide or aluminium magnesium hydroxide gels.

3. A preparation according to claim 1 or 2, wherein the hydroxylated polyalkene has a molecular weight of 950 to 10,000.

4. A preparation according to any one of the preceding claims, wherein the hydrophobic organic substance is a glycerol mono-, di- or tri-ester of palmitic or stearic acid.

5. A preparation according to any one of the preceding claims, wherein the hydrophobic organic substance is a hydrogenated mono-, di-

or tri-glyceride in which 70 - 90 per cent by weight of the ester is a 12-hydroxystearic ester and 10 - 30 per cent by weight of the ester is a stearic acid ester.

6. A preparation according to any one of the preceding claims, wherein the emulsifier is a polyoxyethylene-sorbitan mono-ester of an acid which is oleic, lauric, stearic or palmitic acid.

7. A preparation according to any one of the preceding claims additionally containing a gastric acid secretion inhibitor.

8. A preparation according to claim 7, wherein the inhibitor is cimetidine. ranitidine or omeprazole.

9. A preparation according to any one of the preceding claims in the form of a powder, granulate or chewable tablet.

10. A process for producing a preparation as defined in any one of the preceding claims which comprises forming an emulsion of the hydrophobic organic substance, the hydroxylated polyalkene and the emulsifier and then granulating a powder mixture containing the antacid and excipient with the emulsion.

11. A process according to claim 10, wherein the emulsion is formed by dissolving the hydrophobic substance in an organic solvent, adding the emulsifier to the resulting solution and then emulsifying the hydroxylated polyalkene into the mixture of solution and emulsifier.

12. A process according to claim 11, wherein the emulsion contains 50 - 90 parts by weight of the hydrophobic substance and 10 - 20 parts by weight of the hydroxylated polyalkene, the balance being solvent and emulsifier.

13. A process according to any one of claims 10 to 12, wherein 1 part by weight of the powder mixture is mixed and kneaded with 1 to 3 parts by weight of the emulsion, and a binder is then added to the resulting wet mass and the wet product finally granulated.

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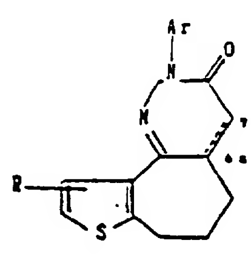
(54) THIENOCYCLOHEPTAPYRIDAZINE COMPOUNDS AND MEDICINAL USES THEREOF.

(57)



(I)

Thienocycloheptapyridazine compounds represented by general formula (I), wherein R represents hydrogen, halogen or C_{1-4} alkyl, Ar represents aryl or heteroaryl which may have at least one substituent selected from among halogen, C_{1-4} alkyl, C_{1-4} alkoxy, nitro, amino, hydroxy, trifluoromethyl and C_{2-5} alkanoyl, and a bond ---- between the 6a-position and the 7-position represents a single or double bond are disclosed. The compounds are useful as an anti-anxiety agent, amnesia treating agent, brain function

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activating agent or dementia treating agent.

SPECIFICATION

Thienocycloheptapyridazine Compounds and their Pharmaceutical Us

[Technical Field]

This invention relates to thienocycloheptapyridazine compounds which are novel and of use as pharmaceuticals and their pharmaceutical use.

[Background Art]

Benzodiazepine (BZP) derivatives represented by diazepam have been used long as an antianxiety drug or a therapeutic medicine for sleep disturbance. The recent pharmacological studies have shown that there exist receptors which exhibit a specific affinity for BZP derivatives in the central nervous system [Science, vol. 198, 849 (1977)]. In the studies and researches conducted subsequently, there have been investigated and developed not only BZP derivatives but also the compounds which have structures different from BZP but exhibit a high affinity for BZP receptors and a BZP-like action (BZP agonist), the compounds which exhibit a high affinity for BZP receptors but exhibit a pharmacological action reverse to BZP (BZP inverse-agonist) and the compounds which exhibit a high affinity for BZP receptors but nevertheless exhibit no pharmacological activity themselves and rather show an antagonistic action against the action of the agonist or the inverse-agonist (BZP antagonist) [Advance in Drug Research, vol. 14, 165 (1985)].

Since BZP derivatives which are used as an antianxiety

drug have a sedative action, a muscle-relaxing action and an anticonvulsive action in addition to an antianxiety action, they often cause troubles in terms of side effects such as dizziness and sleepiness. Thus, researches of non-BZP types of compounds aiming at developing selective antianxiety drugs with less side effects are thriving. Nevertheless, there have not been found satisfactory ones yet.

Also, in recent years, amnesia-inducing actions by BZP agonists were found [Nature, vol. 321, 864 (1986)], and there have been reports suggesting the possibility that BZP-antagonists exhibiting an antagonistic action against the amnesic actions induced by BZP agonists and BZP-inverse-agonists exhibiting an action reverse to the amnesic actions by BZP agonists are usable as brain-function activating drugs. [Trends in Neurosciences, vol. 11, 13 (1988)].

In the meantime, in the specification of U.S. Patent No. 4602019 there are disclosed compounds such as 2,4,4a,5-tetra-hydro-7-(1H-imidazol-1-yl)-3H-indeno[1,2-c]pyridazin-3-one having a cardiac action and an antihypertensive action. The Journal of Medicinal Chemistry, vol. 24, 830 (1981) discloses compounds such as 2-(4-chlorophenyl)benzothiopyrano-[4,3-c]pyrazol-3-one possessing an immune-supressing action.

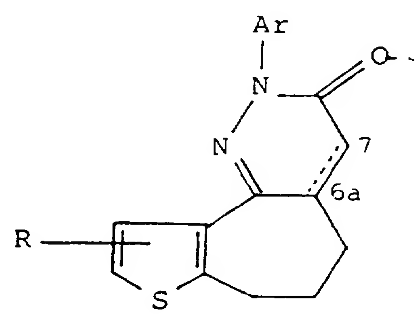
[Disclosure of Invention]

The present inventors have conducted intensive studies for the purpose of developing BZP-agonists, BZP-inverse-agonists or BZP-antagonists having a non-BZP-nucleus which

are useful pharmaceuticals and providing effective compounds and pharmaceuticals.

It has been found that the above-mentioned purpose can be attained according to the present invention described hereinafter.

That is, the first invention is to provide thieno-cycloheptapyridazine compounds of the formula



(I)

wherein R stands for hydrogen, a halogen or a C_{1-4} alkyl, Ar stands for an aryl, a heteroaryl, or an aryl or a heteroaryl having as a substituent at least a halogen, a C_{1-4} alkyl, a C_{1-4} alkoxy, nitro, amino, hydroxy, trifluoromethyl and/or a C_{2-5} alkanoylamino; and the bond ------- between 6a-position and 7-position represents a single bond or a double bond.

The second invention is to provide pharmaceutical compositions comprising a thienocycloheptapyridazine compound of the above formula (I).

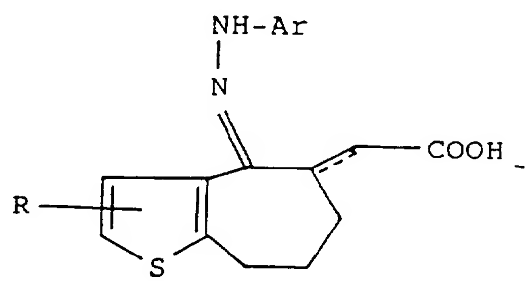
The symbols of the formula (I) and each of the below-mentioned formulae are defined in detail below. The halogen represents chlorine, bromine, fluorine or the like; the C_{1-4} alkyl represents methyl, ethyl, propyl, isopropyl, butyl,

isobutyl or tert-butyl; the C_{1-4} alkoxy represents methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy or tert-butoxy; the C_{2-5} alkanoylamino represents acetylamino, propionylamino, butyrylamino or pivaloylamino; the aryl represents phenyl, naphthyl or the like; and the heteroaryl represents a 5- or 6-membered ring or its fused ring containing 1 to 3 (preferably 1 or 2) hetero atom(s) (e.g. nitrogen, oxygen, sulfur) on the ring such as 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 3- or 4-pyrazolyl, 1- or 2-imidazolyl, 2-, 4- or 5-pyrimidinyl, 3-, 4- or 5-pyridazinyl or 2-, 4- or 5-benzimidazolyl.

Preferable compounds of the present invention are the compounds selected from the group consisting of 9-(4-chlorophenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-phenyl-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methoxyphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6-dihydro-2-methyl-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(6-chloro-2-pyridyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-

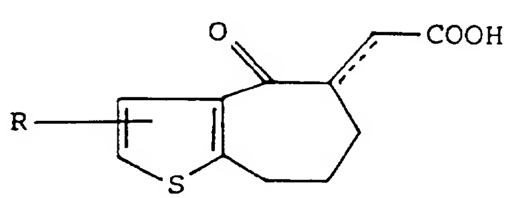
methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta-[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one and 2-bromo-9-(4-chlorophenyl)-5,6-dihydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one.

The compounds of the formula (I) can be produced by subjecting to ring-closure reaction a compound of the formula



(IV)

wherein each of the symbols is as defined above, which can be obtained by reacting a compound of the formula



(II)

wherein R is as defined above, with a hydrazine derivative of the formula

$$Ar - NHNH_2 \qquad (III)$$

wherein Ar is defined as above or its acid addition salt.

The reactions proceed by heating under reflux in a suitable solvent, for example, an alcohol solvent such as methanol, ethanol or propanol, or inert solvent such as benzene or toluene for 5 to 20 hours to yield the compound of the formula (I) and the compound of the formula (IV).

In case where an acid addition salt of the hydrazine derivative of the formula (III) is employed, the reaction is conducted in the presence of an acid scavenger (sodium acetate, potassium acetate, sodium bicarbonate, sodium carbonate, potassium carbonate, pyridine, triethylamine, etc.).

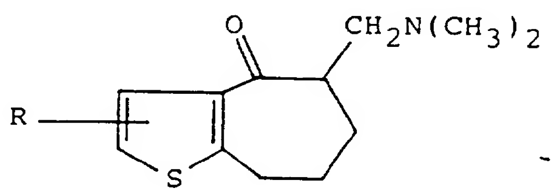
When the compound of the formula (IV) is obtained in the above reaction, the compound of the formula (I) can be produced by heating the obtained compound of the formula (IV) under reflux in acetic acid for 5 - 10 hours.

The compound of the formula (I) wherein the bond between 6a-position and 7-position is a double bond can be synthesized also by adding bromine in an amount of 1 - 1.5 times mol dropwise to the corresponding compound of the formula (I) wherein the bond between 6a-position and 7-position is a single bond in acetic acid as the solvent at 20 - 60°C [Journal of Medicinal Chemistry, vol. 14, 262 (1971)] or by reacting the compound of the formula (I) wherein the bond between 6a-position and 7-position is a single bond with

sodium-m-nitrobenzenesulfonate (Bachmann method, The specification of United Kingdom Patent No. 1168291).

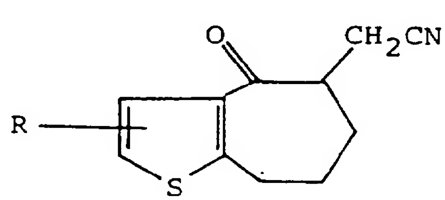
The compounds of the formula (I) which can be produced in the above-mentioned manner can be isolated and purified by a conventional method such as column chromatography or recrystallization.

The compounds of the formula (II) of this invention are novel compounds which have not been described in any literature. The compounds can be produced-by, for example, converting the corresponding compounds of the formula



(V)

wherein R is as defined above, or their acid addition salts to their quaternary ammonium compounds by adding methyl iodide to the compounds of the formula (V) or their acid addition salts in acetone and retaining the mixture at room temperature for 2 - 5 hours, followed by converting the quaternary ammonium compounds to the corresponding cyano compounds of the formula



(VI)

wherein R is as defined above, by adding potassium cyanide or sodium cyanide to the quaternary ammonium compounds in an aqueous methanol and reacting the mixture at 30 - 50°C for 4 - 10 hours, followed by adding the thus-obtained compounds of the formula (VI) to acetic acid and conc. hydrochloric acid and heating under reflux the mixture for 5 - 12 hours.

For reference's sake, representative examples of the compounds of the formula (II) are indicated with their physical constant below.

2-Methyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-5-acetic acid, melting at 155.5 - 157.5°C.

4-Oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-5-acetic acid, melting at 130 - 131°C.

2-Bromo-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-5-acetic acid, melting at 129 - 131°C.

The compounds of the formula (I) exhibit a high affinity of 10^{-8} - 10^{-9} M to BZP receptors and have an antagonistic action against chemical convulsants such as bicuculline and pentylenetetrazole. They also exhibit an inhibitory action against amnesia induced by electroconvulsive shock.

The pharmacological actions of the compounds of the present invention are shown with the experimental methods therefor below.

Experimental Example 1 : Displacement ability for Benzodiazepine

The experiment for specific affinity to benzodiazepine receptors was carried out in accordance with the method described in Life Science, vol. 20, 2101 (1977).

The crude cynaptosome fraction was isolated from the cerebral cortex of male Wistar rats aged 9 - 10 weeks, and was suspended in 50 mM Tris-hydrochloric acid buffer solution (pH 7.4) containing 120 mM sodium chloride and 5 mM potassium chloride. These suspensions were used for the experiment.

The test compounds in several different concentrations and tritiated diazepam (in final concentration of 2 nM) were added to the synaptosome suspensions, and the mixtures were incubated at 0°C for 20 minutes. These suspensions were filtered with Whatman GF/B glassfiber filters. After the filters were washed with the above-mentioned buffer solution, the radioactivity left on the filters was measured with the use of a liquid scintillation counter.

Specific binding was determined by subtracting binding in the presence of 10^{-6} M unlabelled diazepam from total binding.

According to the foregoing experimental method, the binding force to benzodiazepine receptors of the compound of the present invention is evaluated from its displacement ability for tritiated diazepam at its binding site, which is represented by Ki value (nM).

The results of the experiment are shown in Table 1.

Table 1

Test compound (Example No.)	Affinity to BZP Receptors, Ki (nM)
1	4.8
4	1.1

Experimental Example 2 : Anti-Bicuculline Action

The anti-bicuculline action test was carried out in accordance with the method described in Life Science, vol. 21, 1779 (1977).

Male ddY mice weighing 20 - 28 g, 7 - 14 animals per group, were used. One hour after the oral administration of the test compounds, (+) bicuculline was intravenously administered at the dosage of 0.6 mg/kg, and 50% effective concentration (ED_{50}) was estimated by examining whether the tonic convulsion within 5 minutes was caused or not. The result was that the ED_{50} values of the compounds of Example 1 and 5 were 8.1 mg/kg and 9.8 mg/kg, respectively.

Experimental Example 3 : Action on Experimental Amnesia

Twenty male ddY mice were used per each group to investigate the action of the test compounds on learning and memory ability of amnesia-induced mice by observing a step-through passive avoidance reflex. Amnesia-induced animals were prepared by applying electroconvulsive shock (ECS) soon after the acquisition trial and the retention test was carried out 24 hours after the acquisition trial. Test compounds were administered intraperitoneally (i.p.) 30

minutes before the acquisition trial.

As the result, it was found that the compound of Example 4 significantly prolonged the latency time in the trial of the retention test at the dose of 2.5 mg/kg (i.p.) or more and exhibited an improvement action on amnesia.

Experimental Example 4 : Acute Toxicity

Five male ddY mice were used per each group. The mice were administered with 300 mg/kg of the compound of Example 4 intraperitoneally, but all mice survived for 5 days after the administration. Similarly, the mice were orally administered with 1000 mg/kg of the compound, but they survived for 5 days after the administration.

As apparent from the foregoing various pharmacological studies including experiments, the compounds (I) of the present invention have a high affinity for BZP receptors and exhibit an antagonistic action against chemical convulsion-inducing agents such as bicuculline and pentylenetetrazole, whereas they influence to a small extent on somatic functions such as muscle-relaxing actions. Thus, they are useful as an antianxiety agent. Also, since they possess an inhibitory action on amnesia induced by electroconvulsive shock, they are useful as an amnesia-treating drugs, brain function-activating drugs and antidementiac drugs. They are also of value as an antidote for excessive administration of or toxicosis by existent antianxiety drugs such as diazepam.

When the compounds of the formula (I) are used as pharma-

ceuticals, a therapeutically effective amount of the compounds and adequate pharmacologically acceptable additives such as excipient, carrier, diluent and so on are mixed to be formulated into a form such as tablets, capsules, granules, syrups, injectable solutions, suppositories, dispersible powders or the like and are administered in a form mentioned above. The dosage, for example, in the case of oral administration, is generally about 5 - 500 mg daily per adult, which is once a day or in divided doses several times a day administered.

Below, this invention is more specifically described with working examples, which are not to be construed as limitative.

Example 1

A suspension of 2.5 g of 2-methyl-4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-5-acetic acid and 1.95 g of 4-chlorophenyl hydrazine in 50 ml of toluene is refluxed under heating for 4 hours. After cooling, the mixture is concentrated under reduced pressure and the precipitated crystals are recrystallized from ethanol to give 2.7 g of 9-(4-chlorophenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 119 - 121°C.

Example 2

The reaction and procedure are conducted in the same manner as in Example 1 using 4-methylhydrazine in place

of 4-chlorophenylhydrazine as used in Example 1 to give 9-(4-methylphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 117 - 119°C.

Example 3

The reaction and procedure are conducted by the same method as of Example 1 using phenylhydrazine instead of 4-chlorophenylhydrazine as used in Example 1 to give 9-phenyl-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 102 - 103°C.

Example 4

The reaction and procedure are conducted by the same method as of Example 1 using 4-methoxyphenylhydrazine in place of 4-chlorophenylhydrazine as used in Example 1 to give 9-(4-methoxyphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 136 - 138.5°C.

Example 5

To a solution of 3.6 g of 9-(4-chlorophenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one in 30 ml of acetic acid is added 0.6 ml of bromine at 40°C with stirring and the reaction mixture is stirred at 40 - 45°C for 30 minutes. The mixture is poured into water and the resultant oil is collected by decantation. The crude product is subjected to column chromatography on silica gel

and eluted with chloroform to give 1.27 g of 9-(4-chlorophenyl)-5,6-dihydro-2-methyl-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 149.5 - 151°C.

Example 6

A suspension of 2.0 g of 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-5-acetic acid and 1.6 g of 4-chlorophenylhydrazine in 40 ml of ethanol is refluxed under heating for 8 hours. After cooling, the mixture is concentrated under reduced pressure and the ethanol is distilled off. The residue is dissolved in 40 ml of acetic acid and the solution is refluxed under heating for 2 hours. After distilling off the acetic acid under reduced pressure, the resultant residue is subjected to column chromatography on silica gel. The crystals obtained from the fraction which has been eluted with chloroform are recrystallized from a mixed solvent of chloroform and ethanol to give 2.0 g of 9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one as pale brown crystals, melting at 156 - 158°C.

The following compounds can be obtained in the same manner as in the above examples.

Example 7

9-(6-Chloro-2-pyridyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 165 - 167°C.

Example 8

9-(4-Methylphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-

f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 105 - 107°C.

Example 9

9-(4-Methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 135 - 137°C.

Example 10

2-Bromo-9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 129 - 131°C.

Example 11

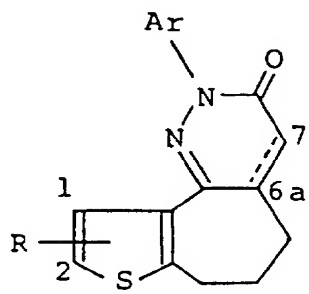
2-Bromo-9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, melting at 139 - 141°C.

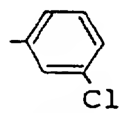
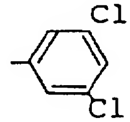
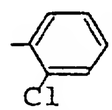
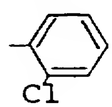
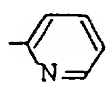
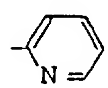
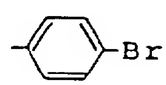
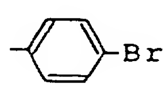
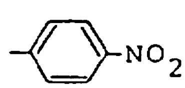
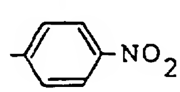
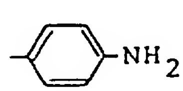
Example 12

To a solution of 2.5 g of 2-bromo-9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one in 40 ml of acetic acid is added a solution of 1.1 g of bromine in 5 ml of acetic acid with stirring at 40°C over a period of 10 minutes. The mixture is stirred at 40 - 50°C for 20 minutes and poured into ice-cold water. The precipitated crystals are collected by filtration, washed with water, dissolved in chloroform and subjected to column chromatography on silica gel. The crystals obtained from the fraction which has been eluted with chloroform are recrystallize from a mixed solvent of ethanol and chloroform to give 1.5 g

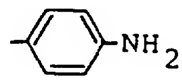
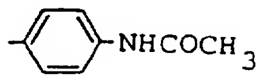
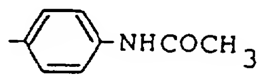
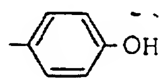
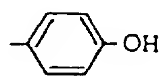
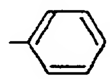
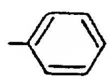
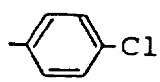
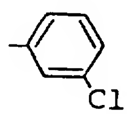
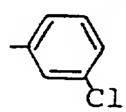
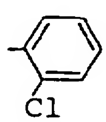
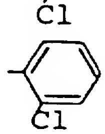
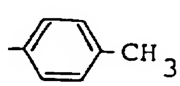
of 2-bromo-9-(4-chlorophenyl)-5,6-dihydro-4H-thieno[2,3-f]-cyclohepta[1,2-c]pyridazin-8(9H)-one as white crystals, melting at 143 - 144°C.

The compounds shown in the following tables can be obtained in the same manner as in the above examples.

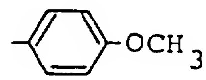
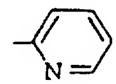
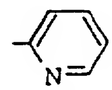
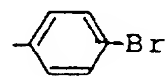
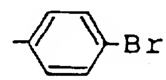
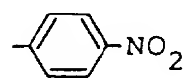
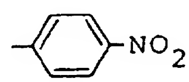
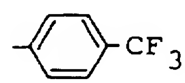
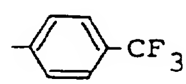
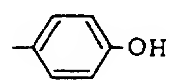
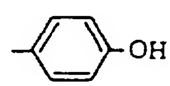
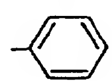
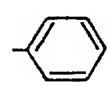


No.	R	Ar	6a-7 bond
13	2-CH_3		S
14	2-CH_3		D
15	2-CH_3		S
16	2-CH_3		D
17	2-CH_3		S
18	2-CH_3		D
19	2-CH_3		S
20	2-CH_3		D
21	2-CH_3		S
22	2-CH_3		D
23	2-CH_3		S

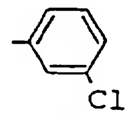
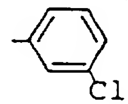
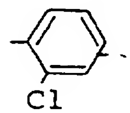
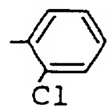
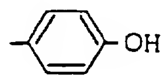
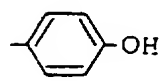
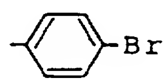
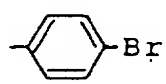
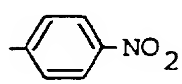
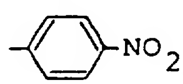
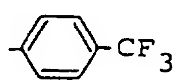
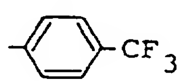
S:single bond, D:double bond

No.	R	Ar	6a-7 bond
24	2-CH_3		D
25	2-CH_3		S
26	2-CH_3		D
27	2-CH_3		S
28	2-CH_3		D
29	H		S
30	H		D
31	H		D
32	H		S
33	H		D
34	H		S
35	H		D
36	H		D

S:single bond, D:double bond

No.	R	Ar	6a-7 bond
37	H		D
38	H		S
39	H		D
40	H		S
41	H		D
42	H		S
43	H		D
44	H		S
45	H		D
46	H		S
47	H		D
48	2-Br		S
49	2-Br		D

S:single bond, D:double bond

No.	R	Ar	6a-7 bond
50	2-Br		S
51	2-Br		D
52	2-Br		S
53	2-Br		D
54	2-Br		S
55	2-Br		D
56	2-Br		S
57	2-Br		D
58	2-Br		S
59	2-Br		D
60	2-Br		S
61	2-Br		D

S:single bond, D:double bond

Formulation Example

Tablets containing 10 mg of a compound of the formula (I) are prepared in accordance with the following formulation.

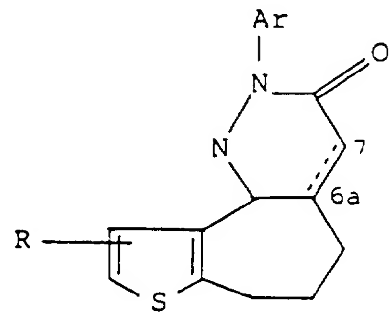
Compound of formula (I)	10.0 mg
Lactose	58.5 mg
Corn starch	25.0 mg
Crystalline cellulose	20.0 mg
Polyvinylpyrrolidone K-30	2.0 mg
Talc	4.0 mg
Magnesium stearate	0.5 mg
	120.0 mg

The compound of the formula (I) is pulverized by an atomizer into fine powders below 10 μ in average particle diameter, which are admixed with lactose, corn starch and crystalline cellulose sufficiently in a kneading machine, and further kneaded with polyvinylpyrrolidone paste. The kneaded mixture is passed through a sieve of 200 mesh, dried at 50°C and passed through a sieve of 24 mesh. Talc and magnesium stearate are mixed therewith and the mixture is compressed into 120.0 mg tablets with a punch of 8 mm in diameter. These tablets are, if desired, subjected to sugar-coating or film-coating.

While the present invention has been adequately and sufficiently described in the foregoing specification including examples, the description can be changed or modified within the spirit and scope of this invention.

Claims

1. A thienocycloheptapyridazine compound of the formula



wherein R is hydrogen, a halogen or a C_{1-4} alkyl, Ar is an aryl, a heteroaryl, or an aryl or a heteroaryl which has as a substituent at least a halogen, a C_{1-4} alkyl, a C_{1-4} alkoxy, nitro, amino, hydroxy, trifluoromethyl and/or a C_{2-5} alkanoyl-amino; and the bond ------ between 6a-position and 7-position is a single bond or a double bond.

2. A compound as claimed in Claim 1 which is selected from a group consisting of 9-(4-chlorophenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-phenyl-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methoxyphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6-dihydro-2-methyl-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-

8(9H)-one, 9-(6-chloro-2-pyridyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one and 2-bromo-9-(4-chlorophenyl)-5,6-dihydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one.

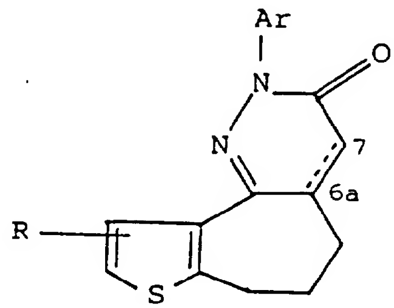
3. A pharmaceutical composition comprising a compound as claimed in Claim 1 or Claim 2 and pharmaceutical additives.

4. An antianxiety drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

5. An amnesia-treating drug, a brain function-activating drug or an antidementiac drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

Claims (amended)

1. A thienocycloheptapyridazine compound of the formula



wherein R is hydrogen, a halogen or a C_{1-4} alkyl, Ar is an aryl, a heteroaryl, or an aryl or a heteroaryl which has as a substituent at least a halogen, a C_{1-4} alkyl, a C_{1-4} alkoxy, nitro, amino, hydroxy, trifluoromethyl and/or a C_{2-5} alkanoyl-amino; and the bond ------ between 6a-position and 7-position is a single bond or a double bond.

2. A compound as claimed in Claim 1 which is selected from a group consisting of 9-(4-chlorophenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-phenyl-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methoxyphenyl)-2-methyl-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6-dihydro-2-methyl-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-

8(9H)-one, 9-(6-chloro-2-pyridyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methylphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-chlorophenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one, 2-bromo-9-(4-methoxyphenyl)-5,6,6a,7-tetrahydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one and 2-bromo-9-(4-chlorophenyl)-5,6-dihydro-4H-thieno[2,3-f]cyclohepta[1,2-c]pyridazin-8(9H)-one.

3. A pharmaceutical composition comprising a compound as claimed in Claim 1 or Claim 2 and pharmaceutical additives.

4. An antianxiety drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

5. An amnesia-treating drug, a brain function-activating drug or an antidementiac drug comprising a compound as claimed in Claim 1 or Claim 2 as an effective ingredient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP89/00956

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl^4 C07D495/04, A61K31/50

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	C07D495/04, A61K31/50

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
T	JP, A, 1-6278 (Yoshitomi Pharmaceutical Industries, Ltd.) 10 January 1989 (10. 01. 89) & WO, A, 8807533 & EP, A, 308515	1 - 5
T	Chemical Abstracts, Abstract No.110(9): 75426s (Arch, Pharm, Cweinheim, Ger), 321(10), 735-8(1988) Garcia-Dominquez, Neftali; Ravina, Enrique; Santana, Lourdes; Teran, Carmen: Garcia-Mera, Gerardo; Orallo, Francisco: Crespo, Manuel; Fontenla, Jose Angel; Abstract of "Pyridazine derivatives. VI. Synthesis and hypotensive activity of 3-hydrazino thieno[2, 3-h] cinnoline and its derivatives")	1 - 5
A	Chemical Abstracts, Abstract No.103(1): 6254c (J. Heterocycl. Chem., 21(6), 1585-8(1984)	1 - 5

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
October 11, 1989 (11. 10. 89)	November 13, 1989 (13. 11. 89)
International Searching Authority	**Signature of Authorized Officer**
Japanese Patent Office	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	Abarca, Belen; Ballesteros, Rafael; Jones, Gurnos: Abstract of "The Synthesis of thienocycloheptenoindoles")	1 - 5
A	Chemical Abstracts, Abstract No.102(13): 113328f (Indian J. Chem., Sect. B, 23B(10), 918-25(1984) De, Asish; Brunskill, John S. A.; Jeffrey, Howard: Abstract of "Studies in sulfur heterocycles part III-syntheses of tricyclic compounds with condensed thiophene rings")	1 - 5

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemical Abstracts, Abstract No.102(3): 24389j (J. Chem. Res., synop., (7), 218-19(1984) Sasaki, Tadashi; Ishibashi, Yukio; Ohno, Masatomi: Abstract of "Molecular design by cycloaddition reactions. Part 43. cycloaddition reactions of silyl enol ethers of 2-acetylfuran and -thiophene and related benzo analogs")	1 - 5
A	Chemical Abstracts, Abstract No.100(5): 33904j (Heterocycles 20(10), 1933-6(1983) Sasaki, Tadashi; Ishibashi, Yukio;	1 - 5

V.☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.☐ Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2.☐ Claim numbers ...., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.☐ Claim numbers ... ., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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1.☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4.☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International Application No PCT/JP89/00956

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	Ohno, Masatomi: Abstract of "Molecular design by cycloaddtion reaction. Part 41. Remarkable difference in the cycloaddtion reactivity between 2-(1-trimethylsilyl-oxyvinyl) furan and -thiophene")	
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V.☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons.

1.☐ Claim numbers . . because they relate to subject matter not required to be searched by this Authority, namely:

2.☐ Claim numbers . . , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.☐ Claim numbers . , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI.☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1.☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4.☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International Application No. PCT/JP89/00956

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Chemical Abstracts, Abstract No.76(17): 94565g (J. Med. chem., 14(11), 1127-9(1971) Remers William A.; Gibs, Gabriel J.; Poletto. John F.; Weiss, Martin J.; Abstract of " Tricyclic heterocycles derived from 4-oxo-4,5,6,7-tetrahydro-thianaphthenes")	1 - 5
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International Application No PCT/JP89/00956

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	Haack formylation of 6,7-dihydrobenzo[b] thiophen-4(5H)-one")	
A	Chemical Abstracts, Abstract No.102(17): 149129f (J. Hetero cycl. Chem., 21(5), 1505-8(1984) Arribas, Enrique; Vega, Salvador: Abstract of "Derivatives of benzo[4,5] cyclohepta[1,2-b]thiophene. 3, Synthesis of 2,3,6,7-tetrahydro-3-oxobenzo[1,2] cyclohepta[3,4,5-hi]thieno[3,4-c] pyridine and 2,3,7,8-tetrahydro-3-oxothieno[2,1-b]cyclohepta[5,6,7-de] isoquinoline")	1 - 5

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International Application No. PCT/JP89/00956

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

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European Patent Office

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number

EP 89 91 0671

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X	EP-A-0 308 515 (YOSHITOMI) * Claims 1,4,5 * -----	1,4,5	C 07 D 495/04 A 61 K 31/50
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 495/00 C 07 D 237/36
	The supplementary search report has been drawn up for the claims attached hereto.		

Place of search	Date of completion of the search	Examiner
THE HAGUE	07-10-1991	SEUFERT G.H.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(87) International publication number : **WO 90/09175 23.08.90 Gazette 90/20**

(54) **USE OF OMEPRAZOLE AS AN ANTIMICROBIAL AGENT.**

(30) Priority : **09.02.89 JP 130311/89**

(43) Date of publication of application : **06.03.91 Bulletin 91/10**

(45) Publication of the grant of the patent : **08.09.93 Bulletin 93/36**

(84) Designated Contracting States : **AT BE CH DE DK ES FR GB IT LI LU NL SE**

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EP 0 414 847 B1

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Description

Field of the Invention

The present invention relates to the new use of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole (generic name: omeprazole) or a salt thereof as an antimicrobial agent and more particularly as an antimicrobial agent, which is particularly active against gram-negative bacteria.

Background of the Invention

In view of the abuse or unscrupulous use of antimicrobial drugs in the treatment of infectious diseases or for other purposes and the consequent emergence of drug-resistant strains, increased incidence of microbial substitution due to disturbance of the bacterial flora, changes in profile of infectious diseases, etc., there has been a constant demand for the development of new antimicrobial agents.

This application is especially directed to the treatment of infections caused by Campylobacter pylori. Campylobacter pylori is a grin-negative spirilliform bacterium which colonises deeply in the gastric mucosa. Treatment with commonly used antibiotics has given insufficient effect.

Prior art

Omeprazole and its pharmaceutically acceptable salts, which are used in accordance with the invention, are known compounds, e.g. from EP 5129 and EP 124495 and can be produced by known processes, for example by the process described in Japanese Patent Application No. 34956/1985.

Outline of the invention

The intensive research undertaken by the inventors of the present invention for accomplishing the above-mentioned object revealed surprisingly that 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole (generic name: omeprazole) and pharmaceutically acceptable salts thereof, which are known to have gastric antisecretory activity known to be an antiulcer drug have excellent antimicrobial activity as well.

Heretofore, it has never been known that omeprazole or any compound analogous thereto has antimicrobial activity.

Predicated on the above finding, the present invention relates to an antimicrobial agent containing omeprazole or a salt thereof as an active ingredient.

The salt of omeprazole is virtually optional in kind but is preferably a pharmaceutically acceptable salt. Examples of such salts include inorganic salts, such as alkali metal salts, e.g. sodium salt, potassium salt etc., alkaline earth metal salts. e.g. calcium salt, magnesium salt etc., ammonium salt, organic salts such as organic amine salts, e.g. trimethylamine salt, triethylinine salt, pyridine salt, procaine acid, picoline salt, dicyclohexylamine salt, N,N-dibenzylethylenediamine salt, N-methylglucinine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)methane salt, phenylethylbenzylamine salt, dibenzylethylenediamine salt.

The antimicrobial agent according to the present invention is particularly active against gram-negative bacteria, especially microaerophilic bacteria, inter alia bacteria of the genus Campylobacter represented by C. pylori, and can be effectively utilized for the prevention and treatment of infectious diseases due to such bacteria in mammalian animals including man, cattle, horse, dog, mouse and rat, in the control and inhibition of environmental pollution, or as a disinfectant.

The antimicrobial agent according to the present invention can be made available in a pharmaceutical formulation comprising one or more active ingredients selected from the group consisting of omeprazole and salts thereof or in a formulation containing optional substances as additives (for example, a carrier).

For the treatment or prevention of bacterial infections, for instance, the antimicrobial agent of the invention is generally administered in the form of a pharmaceutical preparation containing omeprazole as such (i.e. the free base) or a salt thereof as an active ingredient in combination with a pharmaceutically acceptable carrier by the oral, rectal or parenteral route. The carrier mentioned above may be a solid, semi-solid or liquid diluent or a capsule. Compatible dosage forms include various types of tablets, capsules, granules, powders, oral liquids, injections and so on. The proportions of the active ingredient in the total composition is generally 0.1 to 100 weight percent and preferably 0.1 to 95 weight percent. In the case of an injectable preparation, the range of 0.1 to 20 weight percent is particularly preferred. In the case of a preparation for oral administration, the preferred proportion is 2 to 50 weight percent.

In the manufacture of a pharmaceutical preparation for oral administration, the active ingredient can be formulated with a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, starch, amylopectin, a cellulose derivative or gelatin, and a lubricating agent such as magnesium stearate, calcium stearate or polyethylene glycol wax may be further incorporated. The resulting composition is then compressed into tablets. Coated tablets or dragees can be manufactured by coating the core tablets, thus prepared, with a thick sugar solution containing gum arabic, gelatin, talc, titanium dioxide, etc. or a lacquor prepared using a volatile organic solvent or solvent mixture.

Soft gelatin capsules can be manufactured by filling a composition comprising the active ingredient and a known vegetable oil into capsules. Hard gelatin capsules can be manufactured by filling into capsules the granules or pellets each comprising the active ingredient and a solid particulate carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, a cellulose derivative or gelatin.

Preparations for rectal administration are preferably suppositories containing the active ingredient and a neutral oleaginous base, gelatin capsules for rectal administration which contain the active ingredient and a vegetal oil or paraffin oil, and rectal ointments.

Liquid preparations for oral administration can be syrups or suspensions, typically a solution containing 0.2 to 20 weight percent of the active ingredient with the balance being a mixture of sucrose with ethanol, water, glycerol and/or propylene glycol. Optionally, these preparations may additionally contain colors, corrigents, saccharin and, as a thickener, carboxymethylcellulose.

Injections can be manufactured in the form of aqueous solutions, typically an aqueous solution containing a pharmaceutically acceptable water-soluble salt of the active ingredient preferably in a concentration of 0.1 to 10 weight percent. These preparations may further contain a stabilizer and/or a buffer and may be provided in ampules containing various unit doses.

The dosage of omeprazole or a salt thereof depends on individual needs (for example, the patient's condition, body weight, age, sex, etc.) as well as on the method of administration. Generally speaking, the oral dosage may range from 1 to 400 mg as active ingredient per day per adult human and the intravenous dosage may range from 1 to 200 mg per day per adult human, and each may be administered in one to a few divided doses.

Pharmacological data

Experiment 1

The in vitro antimicrobial activity of the active ingredient of the present invention was assayed by the following agar plate dilution method.

A loopful (10^7 cells/ml) of the test strain cultured in Brucella Broth containing 5% of horse serum under 10% carbon dioxide gas for 2 days was inoculated onto Brucella Agar containing 5% horse lysed blood. This medium contained a varying concentration of omeprazole. The inoculated media were incubated at 37°C under 10% carbon dioxide gas for 2 days and the minimal inhibitory concentration (MIC) was determined. The result is set forth in Table 1.

Table 1

Test organism	MIC (µg/ml)
Campylobacter pylori 8005	0.39

EXAMPLES

The following examples are intended to illustrate the antimicrobial agent of the invention in further detail and should by no means be constructed as limiting the scope of the invention.

Example 1 (25 mg tablets)

Omeprazole	250 g
Lactose	175.8 g
Corn starch	169.7 g

The above ingredients are mixed and wetted with 10% gelatin solution, and the wet mixture is sieved through a 12-mesh screen and pulverized. The resulting powder is dried and magnesium stearate is added. This mixture is then compressed into tablets each containing 25 mg of omeprazole.

Example 2 (capsules)

Omeprazole	93.5 weight %
Carboxymethylcellulose calcium	3.7 weight %
Magnesium stearate	1.9 weight %
Light silicic anhydride	0.9 weight %

The above ingredients are mixed thoroughly and filled into capsules.

Example 3 (capsules)

Omeprazole sodium	93.5 weight %
Carboxymethylcellulose calcium	3.7 weight %
Magnesium stearate	1.9 weight %
Light silicic anhydride	0.9 weight %

The above ingredients are mixed thoroughly and filled into capsules in the conventional manner.

Example 4 (injection)

Omeprazole sodium	40 mg
Sterile water to a final volume of	10 ml

The above ingredients are aseptically filled into separate vials to provide an injectable preparation.

Example 5 (capsules)

Pellets without an intermediate layer

I	- Pulverized mannitol	16150 g
	Dehydrated lactose	800 g
	Hydroxypropylcellulose	600 g
	- Microcrystalline cellulose	400 g
II	- Omeprazole	2000 g
	Sodium laurylsulfate	40 g
	Disodium hydrogen phosphate	80 g
	- Distilled water for injection	4400 g

The dry ingredients (I) are mechanically pre-mixed and, then, a granulated liquid component (II) containing omeprazole is added. The resulting mass is kneaded and moistened to a suitable viscosity. The wet mass is processed by means of an extruder to give spherical pellets which are then dried and screened for size selection.

Intermediate-coated pellets

	Omeprazole pellets without an intermediate layer	6000 g
III	- Hydroxypropylmethylcellulose	240 g
	- Distilled water	4800 g

Using a fluidized-bed equipment, the polymer solution (III) is sprayed over the pellets without an intermediate layer. In this operation, the spray gun is positioned over the fluidized bed.

Enteric-coated pellets

Intermediate-coated pellets		500 g
IV	- Hydroxypropylmethylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

Using a fluidized-bed equipment, the polymer solution (IV) is sprayed over the intermediate-coated pellets using a spray gun positioned over the bed. After drying to a moisture content of 0.5%, the enteric-coated pellets are screened for size selection and filled in 225 mg portions into hard gelatin capsules. (The above amount corresponds to 20 mg of omeprazole). Thirty capsules thus manufactured are packed into a tight container together with a desiccant.

Claims

1. Use of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Campylobacter infections.

Patentansprüche

1. Verwendung von 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazol oder eines pharmazeutisch akzeptablen Salzes davon zur Herstellung eines Medikaments zur Behandlung von Campylobacter-Infektionen.

Revendications

1. Utilisation de 5-méthoxy-2- [[(4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]-sulfinyl]-1H-benzimidazole ou d'un de ses sels pharmaceutiquement acceptables pour la fabrication d'un médicament destiné au traitement d'infections par campylobacter.

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(21) Application number: **89911115.7**

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(54) **MATRIX WITH IMMUNOMODULATING ACTIVITY.**

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22.03.89 SE 8901027
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(84) Designated Contracting States: **AT BE CH DE FR GB IT LI LU NL SE**

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Rank Xerox (UK) Business Services
(3.10/3.09/3.3.3)

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Description

The present invention concerns an iscom matrix comprising at least one lipid and at least one saponin with immunomodulating effect, a process for preparing the matrix, a vaccine and a kit comprising the same and new saponins for incorporation in the matrix and a process for preparing the new saponins.

Many microbial and viral antigens can be produced by modern techniques today. Their full promise in vaccines will however not be realized unless they are administered along with an effective adjuvant, an agent that increases antibody and/or cell-mediated immune responses.

The only adjuvants currently authorized for human use in most countries are aluminium hydroxide and aluminum phosphate which have been used for many years to increase antibody responses to e.g. diphtheria and tetanus toxoids. Although these adjuvants are sufficient for many vaccines, studies have shown that other adjuvants, e.g. Freund's complete adjuvant (FCA), and Quil A often are more efficacious in eliciting antibody response and cell-mediated immunity in experimental animals. In fact, they are frequently required for protection. However, FCA produces granulomas at injection sites, which makes them unacceptable for human and veterinary vaccines. In fact, even aluminium hydroxide may give rise to reactions in form of granuloma at the injection site. For these reasons, many attempts are made to develop adjuvants with the efficacy of FCA but without undesirable side effects.

In Morein's EPC Patent Applications Nos. 83850273.0 and 85850326.1, there are described immunogenic complexes between antigenic determinants with hydrophobic regions and glycosides, among them triterpensaponins and especially Quil A, so called iscom complexes. In such an iscom, the amount of Quil A can be about 10-100 times lower and produce the same antigenic effect as when Quil A in free form is mixed with the antigen.

European Patent Application 87200035.1 indicates that the presence of antigen is not necessary for formation of the basic iscom structure, this being possible to form from a sterol, such as cholesterol, a phospholipid, such as phosphatidylethanolamine, and a glycoside such as Quil A.

It has now been discovered that a phospholipid is not needed for the preparation of the basic iscom structure including no antigen. Instead a sterol, such as cholesterol in conjunction with a glycoside such as Quil A are the essential structural components assembled into a complex resembling the typical cage-like iscom structure, so called matrix. It has also turned out that the matrix has immunomodulating effects such as adjuvant or immunosuppressive effect.

The present invention concerns a complex between at least one lipid such as a sterol, preferably cholesterol, and one or more saponins, such as triterpensaponins, especially Quil A or subcomponents thereof which is not a lipid vesicle without any intentional antigens or antigenic determinants for use as an immunomodulating agent. Thus, there is not integrated any antigenic component as is done in an iscom. This matrix has adjuvant effect and can be used mixed together with one or more antigens preferably in multimeric form.

In this iscom matrix there is also possible to integrate other adjuvants with hydrophobic regions. Addition of other lipids may be required to facilitate the inclusion of other adjuvants. Thus the present invention also concerns a complex containing lipids and adjuvants, other than cholesterol and saponins. Such complexes contains the matrix consisting of cholesterol and saponin, preferably Quil A or subcomponents thereof, one or more other adjuvants and one or more lipids other than cholesterol. These are preferably not lipid vesicles or liposomes and have a very special structure in electron microscopy.

Liposomes have been described in the literature and their general structure is well known to biological research workers. Liposomes are vesicles comprising one or more series of lipid layers forming onion-like structures spaced one from another by aqueous material.

The matrix can be injected in an animal or human being as a mixture with the antigen in multimeric form. Alternatively the matrix and the antigen can be injected separately. In this case the best results are obtained if the adjuvant matrix and the the antigen are injected in regions which are drained into the same lymphatic gland. When the adjuvant is presented in multimeric form in a matrix according to the invention the dose of adjuvant may be lowered as compared with when the adjuvant is injected separately in monomeric form or in an undefined form. This implies that toxic side effects caused by adjuvants when used conventionally, i.e. when they are injected alone as such, can be lowered or avoided. The dose of adjuvant can, however, not be lowered as much as is done in the iscom complexes according to the above mentioned patent applications.

When an adjuvant is used in a matrix according to the invention, the antigen is not integrated in the same particle as the adjuvant as is done in an iscom particle according to the above mentioned EPC Patent Applications. This implies that one can use antigens without amphiphatic properties or antigens which can not be forced to expose hydrophobic regions. As an example it can be mentioned that some viruses do not

have amphiphatic proteins, e.g. picornavirus,adenovirus or parvovirus, but they have a form of submicroscopic particle with the antigen presented in several copies, i.e. as multimers.

For such viruses it is more practical to inject them together with the new adjuvant complex than to couple hydrophobic groups to them or create hydrophobic groups by other means (e.g. partial denaturation) and integrate them into an iscom particle.

Typically, the present matrix contains sterol, preferably cholesterol, and one or more saponins in a molar ratio of about 1 to 1 or in a weight ratio of about 1 to 5. The complexes have an open sperical structure consisting of circular subunits or parts of the spherical structure revealed by electron microscopy. They have a sedimentation coefficient of about 20 S.

When other adjuvants are integrated, the lipid-adjuvant-matrix typically contains sterol and saponin in a molar ratio of about 1:1 and the other adjuvants and lipids together make up to about 1 molar. For such a matrix the molar ratio of sterol; saponin; other adjuvant and lipids is about 1:1:1. Thus the molar ratio of sterol; saponin; other adjuvant and other lipids is 1:1:0,1-1; 0,1-1, i.e. additional lipid or adjuvant may be present in the matrix until its molar ratio (or the sum of their molar ratios) is a half that of the saponin and sterol present.

The structure as revealed by electron microscopy is the same as for iscom and matrix (see Figure 1).

The sedimentation coefficient, being dependent on the density of material incorporated into the matrix, is about 12-22 S for matrices containing cholesterol, saponin, other adjuvants and lipids.

The saponins can be any saponin with hydrophobic regions such as those described in R Tschesche and Wulf, Chemie und Biologie der Saponine in Fortschritte der Chemie Organischer Naturstoffe, published by W Herz, H, Grisebach, G W Kirby, Vol 30 (1973), especially the strongly polar saponins, primarily the polar triterpensaponins such as the polar acidic bisdesmosides, e.g. saponin extract from Quillajabark Araloside A, Chikosetsusaponin IV, Calendula-Glycoside C, Chikosetsusaponin V, Achyranthes-Saponin B, Calendula-Glycoside A, Araloside B, Araloside C, Putranjia-Saponin III, Bersamasaponiside, Putrajia-Saponin IV, Trichoside A, Trichoside B, Saponaside A, Trichoside C, Gypsoside, Nutanoside, Dianthoside C, Saponaside D, preferably aescine from Aesculus hippocastanum (T Patt and W Winkler: Das therapeutisch wirksame Prinzip der Rosskastanie (Aesculus hippocastanum), Arzneimittelforschung 10(4), 273-275 (1960) or sapoalbin from Gyposophilla struthium (R Vochten, P Joos and R Ruyssen: Physico-chemical properties of sapoalbin and their relation to the foam stability, J Pharm Belg 42, 213-226 (1968), especially saponin extract from Qulllaja saponaria Molina, primarily the DQ-extract which is produced according to K Dalsgaard: Saponin Adjuvants, Bull off Int Epiz 77 (7-8), 1289-1295 (1972) and Quil A which is produced according to K Dalsgaard: Saponin Adjuvants III, Archiv für die Gesamte Virusforschung 44, 243-254 (1974). Quil A and subfragments thereof are preferred, especially the fragments B2, B3 and B4B described below.

The present invention also provides new glycosylated triterpenoid saponins derived from Quillaja Saponaria Molina of Beta Amyrin type with 8-11 carbohydrate moieties which have the following characteristics:

a) Substance B2 has a molecular weight of 1988, a carbon 13 nuclear magnetic resonance (NMR) spectrum as indicated in Figures 5A and 6A and a proton NMR spectrum as shown in Figures 11A and 12A.

b) Substance B3 has a molecular weight of 2150 and has a carbon 13 NMR spectrum as shown in Figures 5B and 6B, and a proton NMR spectrum as shown in Figures 11B and 12B.

c) Substance B4B has a molecular weight of 1862, a carbon 13 NMR spectrum as shown in Figures 5C and 6C, and a proton NMR structure as shown in Figures 11C and 12C.

Compounds B2 and B3 have adjuvant activity in their own right. The present invention also relates therefore to the use of these compounds as adjuvants. Compound B4B is of use in the preparation of an iscom matrix. B2 and B3 having adjuvant activity can be included in the matrix.

Matrix can be produced from a sterol such as cholesterol and the saponin B4B. Such a matrix does not seem to have any potent adjuvant activity. In order to potentiate the adjuvant activity in this matrix, it is possible and even preferable to integrate the saponins B2 and/or B3 and/or any other substance with adjuvant effect and with hydrophobic groups. If the adjuvants do not contain any hydrophobic groups such groups might be coupled to them by use of known chemical methods. If other adjuvants than B2 or B3 are to be integrated, there are preferably incorporated further lipids as listed on page 13, last paragraph and paragrahs 1-3 on page 14.

In the sterol-B4B matrix, it is also possible to integrate immunosuppressive substances containing hydrophobic groups or to which such groups have been coupled.

It is also possible to use the sterol-B4B matrix as an immunomodulating agent in mixture with adjuvants, immunosuppressive substances or antigens or mixtures thereof.

As immunodulating agents are considered substances that enhance, suppress or change the immune system such as adjuvants, suppressors, interleukins, interferons or other cytokins.

The invention preferably concerns an matrix containing a sterol, especially cholesterol, B4B and either of B2 and B3 or both. When matrix is prepared from cholesterol and Quil A, it comprises B2, B3 and B4B.

The matrices can be produced by solubilizing at least one sterol in a solvent, adding the saponin or saponins, and possibly the other adjuvants and lipids, whereafter the solvent might be removed and the matrix transformed into a solution where its components are not soluble, e.g. a water solution. This can be done with gel filtration, ultra filtration, dialysis or electrophores. The matrices may then be purified from excess of sterol and Quil A e.g. by centrifugation through a density gradient, or gel filtration. As solvent there might be used water or the solubilizing agents or detergents mentioned below.

The only limiting factor for matrix formation to take place is the time needed in different physico-chemical environments, the major rate limiting factor being the poor solubility of the sterol, e.g. cholesterol, in water, in which the matrix forming saponins are freely soluble.

Thus it has been shown that with Quil A and cholesterol even in solid phase matrix-like formation takes place after a relatively long time, e.g. about 1 month. Cholesterol must be brought into contact with Quil A or its purified components. If the cholesterol is brought into colloidal water suspension through treatment by ultrasonication and treatment by ultra-turrax, matrix is formed with Quil A after about 12 hours.

Consequently, any other substance such as a detergent added to the water, and which will increase the solubility of cholesterol in the aqueous medium, will decrease the time needed for the formation of matrix. It is thus possible to produce a matrix from cholesterol, water and Quil A or the subcomponents thereof, if the cholesterol is brought to a colloidal form. It is, however, more practical to add a detergent or a solvent.

Preferably the saponins are used from a concentration of at least their critical micelle formation concentration (CMC). For Quil A this implies a concentration of at least 0,03 % by weight.

As solubilizing agent there can be used detergents such as non-ionic, ionic i.e. cationic or anionic or Zwitter-ionic detergent such as Zwittergent or detergent based on gallic acid which is used in excess. Typical examples of suitable non-ionic detergents are N-alkanoyl-N-alkyl-glucamines, polyglycol esters and polyglycol ethers with aliphatic or aralylphatic acids and alcohols. Examples of these are alkylpolyoxyethylene ethers with the general formula $C_nH_{2n+1}(OCH_2CH_2)_xOH$ shortened to C_nE_x; alkylphenyl polyoxyethylene ethers containing a phenyl ring between the alkyl group and the polyoxyethylene chain, abbreviated $C_n\phi E_x$, e.g. Triton X-100 = tert.-$C_8E_{9,6}$ (octylphenolether of polyethylene oxide), acylpolyoxyethylene esters; acylpolyoxyethylene sorbitane esters, abbreviated C_n sorbitane E_x, e.g. Tween 20, Tween 80, β-D-alkylglucosides, e.g. β-D-octylglucoside. Typical examples of suitable ionic detergents are gallic acid detergents such as e.g. cholic acid, desoxycholate, cholate and CTAB (cetyltriammonium bromide). Even conjugated detergents such as e.g. taurodeoxycholate, glycodeoxycholate and glycocholate can be used. Other possible solubilizing agents are lysolecithin and synthetic lysophosphoilipids. Even mixtures of the above-mentioned detergents can be used. When using the dialysis method the detergents should be dialysable in not too long time.

Some surface active substances greatly facilitate matrix formation. These include the intrinsic biological membrane lipids with a polar head group and a non-polar aliphatic chain e.g. phosphatidyl choline (negatively charged) and phosphatidyl ethanolamine (positively charged).

Solubilizing can also be performed with alcohols, organic solvents or small amphiphatic molecules such as heptane-1,2,3-triol, hexane-1,2,3-triol or caotrophic substances, acetic acid, such as trifluoro-acetic acid, trichloro-acetic acid, urea or quanidine hydrochloride.

Preferably to be used are ethyl alcohol, dioxane, ether, chloroform, acetone, benzene, acetic acid, carbon disulphid, MEGA-10 (N-decanoyl-N-methyl glucamine) and β-octylglucoside.

Various yields of matrix can be obtained with these substances, and the overall picture is that more matrix is formed the higher the concentration of the detergent is in the system.

It is technically possible to produce, purify, and sterilize matrix in any of the systems described. Therefore the adjuvant active technical preparations of matrix may contain solubilizing agents if their chemical nature and their concentration is acceptable in the final product, e.g. for vaccine purposes. However, in many cases it will be necessary to remove the solubilizing agent from the matrix by dialysis, ultrafiltration or column chromatographic techniques. It is even possible to dilute the preparation until an allowed concentration of a given solubilizing agent or detergent is reached. The preparation is diluted with water or a physiologically acceptable solution preferably to a concentration below the CMC for the solubilizing agent or detergent in the system (the preparation) used.

The solubilizing agent might be incorporated in the matrix in a molar ratio of sterol; saponin; further lipid adjuvants or solubilizing agent 1:1:1, i.e. molar ratio of the sum of lipid, adjuvants and solubilizing agent is up to half the molar that of saponin and sterol.

The solubilizing agent might alternatively be left mixed with the iscom matrix. In order to be integrated the solubilizing agent and other immunomodulating components, should have at least one hydrophobic region. If not present such hydrophobic regions can be coupled to the components before the matrix is made.

Examples of adjuvants that can be incorporated in iscom matrix are any adjuvant, natural or synthetic, with desired immunomodulatory effect, e.g. muramyl dipeptide (MDP)-derivatives, such as fatty acid, substituted MDP, threonyl analogs of MDP; amphipatic copolymers, aliphatic amines such as avridine or DDA, poly anions such as Dextran sulphate, lipopolysaccarides such as saponins (other than Quil A). ("Future prospects for vaccine adjuvants", Warren, H.S. (1988) CRC Crit. Rev. Immunol. 8:2, 83-101; "Characterization of a nontoxic monophosphoryl lipid A", (1987) Johnson, A.G. et al, Rev. Infect. Dis. 9:5, 5512-5516; "Developmental status of synthetic immunomodulators", Berendt, M.J. et al (1985), Year Immunol. 193-201; "Immunopotentiating conjugates", Stewart-Tull, D.E., Vaccine, 85, 3:1, 40-44).

These four references are hereby incorporated as references.

The following zwitterionic, neutral, positive and negative detergents are examples of detergents that have immunomodulating, especially adjuvant activity:
Nonionic block polymer surfactants containing hydrophilic polyoxyethylene (POE) and hydrophobic polyoxypropylene (POP) that differed in mol weight percentage of POE and mode of linkage POP to POE (BASF Wyandotte Corp.), such as L72, L81, L92, pluronic L101, L121, 2531 and 31R1; octablocks T1501; B-D-octylglucosid; catjonic surfactants such as dimethyldioctadecylammonium bromide (DDA), octadecylamine (OCT), and cetyltrimethylammonium bromide (CTAB); maltostose tetrapalmitate, trehalose monomycolate, trehalose dibehenylbehenate; zwittergent detergents (N-alkyl-N,N-dimethyl--ammonio-3-propanesulphonate) Z3-8, Z3-10, Z3-12, Z3-14, Z3-16, obtained from Calbiochem (La Jolla, CA, USA); Z3-18 obtained from Serva (Heidelberg, FRG), Myrj 45, Brij 52, Brij 58 (also from Serva), and dioctylsulphosuccinate and Tween 20, Tween 80, Triton X-100 and sodium deoxycholate.

These detergents can be used as both detergents and adjuvants and be incorporated in the iscom matrix.

The following are examples of immunosuppressive agents that can be incorporated in a sterol (preferably cholesterol) B4B matrix: cyclosporin A, diodecyl dimethyl ammonium bromide, cationic single chain amphiphiles with more than 10 carbon atoms and preferably more than 15 carbon atoms, double chain amphiphiles with up to 14 carbon atoms, preferably up to 12 carbon atoms.

In the case a desired adjuvant or immunosuppressive agent do not have suitable hydrophobic properties, it has to be modified to comprise a hydrophobic domain for incorporation into the matrix.

The hydrophobic group that can be coupled to non-hydrophobic adjuvants are straight, branched, saturated or unsaturated aliphatic chains having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25 carbon atoms, such as lipids, preferably 6, 7 and 8 carbon atoms; small peptides with 1, 2, 3, 4 or 5 amino acids, preferably 2, 3, 4, selected from Trp, Ile, Phe, Pro, Tyr, Leu, Var, especially Tyr; choline acid, ursodesoxycholine acid or cholesterol derivatives.

These hydrophobic groups must be bonded to a group that can be coupled to the non-hydrophobic protein such as carboxyl-, amino-, disulphide-, hydroxyl-, sulphydryl- and carbonyl group, such as aldehyde groups.

As hydrophobic groups that can be coupled are selected preferably carboxyl, aldehyde, amino, hydroxyl, and disulphide derivatives of methane, ethane, propane, butane, hexane, heptane, octane and peptides containing Cys, Asp, Glu, Lys, preferably octanal and Tyr.Tyr.Tyr-Cys, -Asp or -Glu. The hydrophobic groups with a group that can be coupled must be dissolved in water with the aid of for example the solubilizing agents and detergents mentioned above or hydrochloric acid, acetic acid, 67% by volume acetic acid, caustic liquor, ammonia, depending on what substance is to be dissolved. pH is then adjusted to the neutral direction without the substance precipitating; here it is to make sure that there is not obtained a pH-value that denaturates the protein to which the hydrophobic group is to be coupled.

Hydrophobic groups with a carboxyl group as coupling molecule can be coupled to the adjuvants through water-soluble carbodiimides or composite anhydrides. In the first case the carboxyl group is activated at pH 5 with carbodiimide and mixed with the protein dissolved in buffer pH 8 with a high phosphate content. In the latter case the carboxy compound is reacted with isobutylchloroformate in the presence of triethylamine in dioxane or acetonitrile, and the resulting anhydride is added to th protein at pH 8 to 9. It is also possible to convert the carboxyl group with hydrazine to hydrazide which together with aldehydes and ketones in periodate-oxidized sugar units in the protein gives hydrazone bonds.

The amino groups with nitrous acid can at low temperature be converted to diazonium salts, which gives azo bonds with Tyr, His and Lys.

The hydroxyl groups with succinic anhydride can be converted to hemisuccinate derivatives which can be coupled as carboxyl groups.

Aldehyde groups can be reacted with amino groups in the protein to a Schiff's base.

Several coupling groups and methods are described in Journal of Immunological Methods, 59 (1983) 129-143, 289-299, Methods in Enzymoloy Vol 93 pp 280-33, and in Analytical Biochemistry 116, 402-407 (1981) which are here incorporated as references.

The lipids other than sterol can be fats or fat resembling substances such as triglycerides or mixed triglycerides containing fatty acids with up to 50 carbon acids such as saturated fatty acids with 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30 carbon atoms e.g. butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, or unsaturated fatty acids with up to 30 carbon atoms, such as hexadecene acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid; hydroxy-fatty acids such as 9,10-dihydroxy stearic acid, unsaturated hydroxy fatty acids such as castor oil, branched fatty acids; glycerol ethers, waxes i.e. esters between higher fatty acids and monohydric alcohols; phospholipides such as derivatives of glycerol phosphates such as derivatives of phosphatidic acids i.e. lecithin, cephalin, inositol phosphatides, spingosine derivatives with 14, 15, 16, 17, 18, 19 and 20 carbon atoms; glycolipids isoprenoids, sulpholipids, carotenoids, steroids, sterols, cholestanol, caprostanol, phytosterols, e.g. stigmasterol, sitosterol, mycosterols, e.g. ergosterol, bile acids e.g. cholic acid, deoxycholic acid, chenodeoxycholic acid, litocholic acid, steroid glycosides, esters of vitamine A, or mixtures thereof.

These and other useful lipids are described in: Lipid biochemistry and introduction, Ed. M.I. Gurr, A.I. James, 1980, Chapman and Hall, London, New York, University Press Cambridge, which hereby is incorporated as a reference.

Preferably cholesterol phosphatidylcholine, liposomes or intralipid® (Oleum soya fractionate 200 g, Lechitinum fractionate vitello ovi 12 g, glycerol 22.5 g, and H_2O up to 1 liter) are used.

The lipids can be added at any stage in the process, preferably before the addition of the saponin but lipids could also be added after the saponin.

The matrix is best produced by the dialysis method as follows.

Cholesterol dissolved in 20% MEGA-10 or any other suitable detergent, preferably a detergent that can be removed by dialysis, e.g. β-octylglucoside, (in H_2O or a suitable buffer) is mixed with 5 times as much Quil A (solid or dissolved in water or a suitable buffer, e.g. PBS). The mixture is dialysed extensively against PBS, first over night at room temperature (because MEGA-10 will precipitate at +4 °C), then at +4 °C. The matrixes are purified from excess Quil A and cholesterol by pelleting through e.g. 30% (w/w) sucrose (e.g., a TST 41.13 rotor 18 h, 39.000 rpm, 10 °C). The pelleted matrices are dissolved in PBS (or any other suitable buffer) and the concentration adjusted to 1 mg/ml).

The present matrix can be used as an immunomodulating substance. It can be used as a potentiating agent for an immunosuppressive substance or an adjuvant, either mixed therewith or integrated in the matrix.

A matrix containing a sterol such as cholesterol, saponins, adjuvants and optionally further lipids can be used as an adjuvant. It can be used for potentiating the antigenic effect of any antigen or antigenic determinants from any pathogenic organism or any fragments or subunits of, or derived from these. Thus it can be used as an adjuvant for those antigens that are integrated in an iscom. Such antigens are mentioned in the EPC-patent applications 83850273.0 and 85850326.1, which are hereby incorporated as references. Thus the matrix can be used as adjuvants together with antigens or antigenic determinants derived from viruses with or without envelope, bacteria, protozoa, mycoplasmas, helminths, mollusca or together with such whole organisms. The antigens or antigenic determinants might further be hormones, enzymes, carbohydrates and carbohydrate-containing structures such as lipopolysaccharides, peptides or proteins or recombinants thereof.

The present invention thus also covers human or veterinary medicine, characterized in that it comprises at least one matrix and one or more antigenic or immunosuppressive substances and a pharmaceutically acceptable vehicle in mixture or in separate compartments.

The invention also concerns a vaccine comprising an matrix, one or more antigens and a pharmaceutically acceptable vehicle.

Further the invention concerns a kit comprising such a medicine or vaccine.

In some medicines or vaccines the detergent used when preparing the matrix can be present if the detergent is allowed for the product in question.

The effect of the new adjuvant complex according to the invention will now be described in immunostimulating experiments.

1. Comparison between the immunogenic effects from antigens presentated as iscoms, micelles or micelles plus the new matrix.

Mice were immunized with envelope protein from influenza virus in the form of iscom complex, micelles and micellas together with the new complex according to the invention (so called matrix). The immune response was evaluated by measuring the antibodies with ELISA technique 15, 30, 44 and 50 days after injection. The following injections were made:

1. 5 µg Micell 1 0,1 µg matrix were mixed and injected in the left foreleg.
2. 5 µg Micell + 0,1 µg matrix injected separately in the right and left foreleg respectively.
3. 5 µg Micell
4. 5 µg iscom prepared according to EPC 83850273.0

TABLE 1

DAY	1	2	3	4
15	23.700 ± 9.500	12.900 ± 14.500	18.900 ± 9.500	41.600 ± 1.000
30	30.800 ± 10.500	8.800 ± 7.100	9.800 ± 3.600	80.700 ± 21.700
44	30.000 ± 17.600	32.600 ± 17.300	17.900 ± 4.200	129.100 ± 78.400
50	309.300 ± 89.000	136.700 ±103.700	87.600 ± 18.200	880.430 ±295.500

No side effects in the form of local reactions were noted.

From this experiment one can conclude that envelope protein from influenza in the form of iscom or micelles plus matrix gives the highest antibody titres. Matrix can be presented in a very low dose and still have adjuvant effect. In order to get an adjuvant effect in mice, Quil A in free form is required in a dose a 100 times the dose of matrix, i.e. 10 µg. With that dose Quil A begins to give local side reactions. On order for matrix to have an obvious adjuvant effect the antigen in multimeric form should be injected in the same region e.g. leg as the matrix, i.e. the injected adjuvant matrix complex and antigen should be presented in a region, that is drained to the same lymphatic gland.

2. Comparison between the immunogenic effects from envelope protein from influenza in the from of iscom or micelle with or without matrix or diphteriatoxoid (DT).

Mice were injected with envelope protein in the following forms:

1. 5 µg Iscom + 5 µg DT
2. 5 µg Iscom
3. 5 µg micelle
4. 5 µg micelle + 0,1 µg matrix

The antibody response on envelope proteins was estimated in the serum with ELISA-technique.The following results were obtained:

TABLE 2

DAY	1	2	3	4
15	52.800 [1)]	48.300	8.400	29.000
30	119.202	155.567	22.107	87.000
50	110.600	136.200	33.400	96.500
65	1.691.000	3.783.000	283.300	1.149.000
80	562.800	2.529.000	512.300	976.500

[1)] ELISA-titer where the last dilution gives a significant positive value at 450 nm.

No visible side effects in form of local reactions could be noted.

One can conclude that envelope protein from influenza virus in the form of iscom or micelles plus the adjuvant complex (matrix) according to the invention gives the highest antibody titres. The dose of matrix can be kept very low, i.e. 0,1 µg, and still has a notable adjuvant effect.

3. Comparison between the immunogenic effects from diphtheria toxoid (DT) in monomeric form, monomeric DT + iscom containing envelope protein from influenza virus, monomeric DT in mixture with Quil A and cholesterol and monomeric DT + adjuvant complex (matrix) according to the invention.

In this experiment diphtheria toxoid is used as a model antigen in monomeric form.

Mice were injected with diphtheria toxoid in the following forms:

1. 5 μg DT (diphtheria toxoid)
2. 5 μg DT + 5 μg iscom
3. 5 μg DT + 0,5 μg Quil A + 0,1 μg CL (cholesterol)
4. 5 μg DT + 0,1 μg matrix

TABLE 3

DAY	1	2	3	4
15	≦ 30	≦ 30	≦ 30	≦ 30
30	≦ 30	≦ 30	≦ 30	≦ 30
50	≦ 30	≦ 30	≦ 30	≦ 30
65	≦ 30	90	≦ 30	10.000
80	≦ 30	60	90	1.100

The immungenic response to DT is low in all the groups. The best result is obtained with mice immunized with diphtheria toxoid plus matrix according to the invention.

From the experiments above one can conclude that the best results are obtained when the matrix according to the invention is used together with the antigen in multimeric form. The matrix according to the invention has thus proved to give very good results as adjuvant compared with e.g. Quil A in free form. Thus it is worth noting that Ouil A is effective as adjuvant in free form in doses such as 10 μg for mice, 50 μg for guinea-pigs and 1 mg for cattles. A practical volume for injection of a vaccine is 1 ml for small animals and 2 to 5 or 10 ml for big animals. As CMC (the critical micelle concentration) for Quil A is 0,03%, 1 ml will imply an amount of 300 μg when 1 ml is injected. After injection, however, due to the dilution effect, the concentration will become lower than CMC and the micelle will become unstable.

According to the present invention, however, the saponin and especially the Quil A molecules will be bounded together with cholesterol molecules so that a relatively stable complex is formed at very low concentrations. This complex is effective as adjuvant in a dose, which corresponds to 0,1 μg Quil A, i.e. 100 times lower than when Quil A is presented in free form.

The Figures show:

Fig. 1 shows an electron microscope picture of a typical matrix;

Fig. 2 shows U.V. eluation profiles for subfractions of Quil A;

Fig. 3 demonstrates HPTLC-separation of Quil A and its subfractions;

Fig. 4 shows FAB-mass-spectra for the new substances according to the invention;

Fig.:s 5 and 6 show ^{13}C-NMR-spectra (2-regions) for the new substances;

Fig.:s 7, 8 and 9 show complete ^{13}C-NMR-spectra for B2, B3 and B4B, respectively;

Fig. 10 shows the β-amyrin-skeleton;

Fig.:s 11 and 12 show the ^{1}H NMR-spectra for the new substances;

Fig. 13 shows parts of the spectra in Fig.:s 7 and 8; and

Fig. 14 shows a 2-dimensional NMR-spectrum for substance B3.

The invention will now be described further with the following example.

Example 1:

Matrix (Cholesterol-Quil A complex)

1 mg of cholesterol dissolved in 20 % MEGA-10 (in H_2O) was mixed with 5 mg of solid Quil A. The Quil A was dissolved and the mixture was dialysed extensively against PBS, first over night at room temperature, then at +4°C. The iscom matrixes were purified from excess Quil A and cholesterol by pelleting through 30 % (w/w) sucrose (TST 41.13 rotor 18 h, 39.000 rpm, 10°C). The pelleted matrixes were dissolved in PBS and the concentration adjusted to 1 mg/ml (traced by a small amount of ^{3}H-cholesterol).

Example 2:

MDP (muramyldipeptide, Sigma, adjuvant peptide) was conjugated to phosphatidyl ethanolamine (PEA) using N-ethyl-N'-(dimethyl-aminopropyl) carbodiimide hydrochloride as described by Lefrancier et al., 1977 (Lefrancier, P., Choay, J., Derrien, M. and Lederman, I. (1977) Int. J. peptide Protein Res. 9:249-257).

To 1 mg of cholesterol (in 20% MEGA-10 in H_2O) was added an equimolar amount of MDP-PEA (in MEGA-10 or DMSO or any other water miscible solvent), an equimolar amount of phosphatidyl choline and 7 mg of Quil A (a slight excess in comparison to 5 mg that is required for IM-formation). After a short incubation at room temperature (15-30 min) the mixture was extensively dialysed against PBS (room temperature 4-12 h, then at +4°C).

After completed dialysis, the matrix-complexes with the additional adjuvant integrated were purified from excess Quil A by pelleting through 10% sucrose.

Example 3:

To 1 mg of cholesterol (in 20% MEGA-10 in H_2O) was added an equimolar amount of Avridine (N,N-dioctadecyl-N'N'-bis(2-hydroxyethyl)propenediamine (in MEGA-10 or DMSO or any other water micible solvent), an equimolar amount of phosphatidyl choline and 7 mg of Quil A (a slight excess in comparison to 5 mg that is required for IM-formation). After a short incubation at room temperature (15-30 min) the mixture was extensively dialysed against PBS (room temperature 4-12 h, then at +4°C).

After completed dialysis, the matrix-complexes with the additional adjuvant integrated were purified from excess Quil A and adjuvant by pelleting through 10% sucrose (the same method as described on page 14, last paragraph).

Example 4:

To 1 mg of cholesterol (in 20% MEGA-10 in H_2O) was added an equimolar amount of DDA (dimethyl dioctadecyl ammonium bromide (in MEGA-10 or DMSO or any other water micible solvent), an equimolar amount of phosphatidyl choline and 7 mg of Quil A (a slight excess in comparison to 5 mg that is required for matrix-formation). After a short incubation at room temperature (15-30 min) the mixture was extensively dialysed against PBS (room temperature 4-12 h, then at +4°C).

After completed dialysis, the matrix-complexes with the additional adjuvant integrated were purified from excess Quil A and adjuvant by pelleting through 10% sucrose (the same method as described on page 14, last paragraph).

Example 5:

2 g of Mega 10 is added to 10 ml of water before the addition of 200 mg cholesterol, and the cholesterol is dispersed by ultrasonication/ultraturrax. As much as 1.6 ml of this mixture can be added to the 10 ml of 2% Quil A-solution. The reaction mixture clarifies completely after less than one hour indicating that all the cholesterol has been reacted. It can be seen in the electron microscope that the concentration of matrix is very high even if the concentration of detergent in this case is 10%. Removal of the detergent by dialysis or ultrafiltration does not quantitatively affect the number of matrix particles, and the solution of matrix stays completely clear.

This experiment indicates that matrix formation takes place when the surfactants are present in the reaction mixtures, and that complete matrix formation takes place in very high concentrations of detergent.

Example 6:

Preparation of the Quil A components B2, B3 and B4B according to the invention.

5 g Cortex quillajae (Nordiske Droge of Kemikalieforretning, Copenhagen, Batch nr 8372) and 50 ml destillated water was mixed by a magnetical stirrer for 3 hours at room temperature. The liquid phase was separated through a Büchner funnel by a filter paper and was purified by filtering through a Metricel Gelman membrane 0.22 μ. Such an extract contains 2.5% dry material.

The crude extract was dialysed against 200 volumes of destillated water in a Visking-tube without weld 20/32 for 48 hours with exchange of water after 24 hours. This extract is called DQ.

The dialysed extract above was subjected to ion exchange chromatography. A column of DEAE-cellulose equilibrated with 0.1M Tris-HCl pH 7.5 was prepared (Whatman DE52) in a K 9/15 column (Pharmacia Fine Chemicals). The bed material was equilibrated with 0.1M Tris-HCl buffer pH 7.5. The column was eluted either stepwise or by a linear salt gradient at a flow rate of 60 ml/h using a peristaltic pump. 50 ml DQ was introduced on the column and 300 drop (equivalent to approx. 5 ml) fractions were collected. Under these conditions, some of the substances in DQ passed unbound through the column, as will be seen from Fig. 2A (peak A). Elution was continued until no UV absorption was detectable. The absorption of the effluent liquid was recorded at 280 nm by a Uvicord II system (LKB-Produkter), and fractions were collected by a Golden Retriever (ISCO). At this point a buffer containing 0.2M NaCl made up in start buffer was introduced. As can be seen in Fig. 2A, a peak B is eluted. However, some substances were still attached to the bed material to such a degree that elution was difficult even with concentrated NaCl. These substances were the ones that contributed to the brownish colour of DQ, whereas peak A and B were only slighly coloured or completely colourless, respectively. In the next purification step, peak B was pooled and subjected to gel exclusion chromatography on Sephadex G50 fine equilibrated with M/50 phosphate buffer pH 7.5 in a K 16/70 column eluted at a flow rate of 10 ml/h. Desalting was carried out on Sephadex G25 medium in a K 16/40 column. Elution was carried out using a hydrostatic head of 50 cm. As will be seen from Fig. 2B, the UV profile showed 3 peaks. Peak C was eluted in the void volume (as determined by Blue Dextran 2000, Pharmacia Fine Chemicals) and peak E was eluted in the total volume of the column (also determined by potassium chromate). Peak D was well separated from peak C and E, but as can be seen in Fig. 2B, the presence of a shoulder indicated that peak D consisted of at least two substances.

Consequently, peak D was pooled and subjected to a new separation on DEAE-cellulose. The starting conditions were the same as in the first ion exchange experiment, and as a result all the material was adsorbed to the column. Elution was now continued with a linear NaCl gradient increasing from 0 to 1 molar (made up in the start buffer) in the course of 300 ml. The result of this experiment is shown in Fig. 2C. Two peaks F and G appeared in the UV profile. F was clearly separated and a single substance (section 3.3), but peak G could not be isolated since it was contaminated with F. In order to investigate the homogeneity of peak F, it was pooled, desalted on Sephadex G25, and rechromatographed in an identical experiment. As can be seen from Fig. 2D, only one symmetrical peak (H) appeared at the position of peak F.

Anyone of the fractions (also the DQ-extract) can be further purified as follows.

Fraction H was lyophilized and dissolved in chloroform/methanol/H_2O (60:40:9, v/v/v). 200 mg was then applied to an HPLC column (4.5x50 cm) packed with silicic acid, latro-beads RS-8060 (latron Labs, Tokyo, Japan). A pump speed of 5 ml/min was used for pumping a total of 2 L solvent, collecting 200 fractions of 10 ml with a gradient of chloroform/methanol/H_2O (60:40:9 to 50:40:10). The fractions were analyzed with thin layer chromatography in the following way. 2 μl of every second fraction was analyzed by developing thin layer liquid chromatography plates (TLC-plates) (HPTLC, Merek, Bodman Chemicals, Gibbstown, NJ) in chloroform/methanol/0.2% $CaCl_2$ (50:40:10 v/v/v) and the glycosides were determined by being green-coloured with anisaldehyde reagent (acetic acid/sulphoric acid/paraanisaldehyde (98:2:1)). The Quil A starting material was used as a reference of the R_f-value. (See Fig. 3, which shows a HPTLC-separation of: lane 1, Quil A (fraction H); lane 2, B1; lane 3, B2; lane 4; B3; lane 5, B4A; and lane 6, B4B).

Fractions that comigrate with B2, B3 and B4B having identical R_f-values were pooled and analyzed for purity with TLC. These crude fractions usually must be chromatographed two times in order to become pure enough. Fractions B1 and B4A are inactive and therefore are not separated further.

The thus enriched components were further purified on an HPLC column (21.2x250 mm) packed with 5 μ spherical silica particles (Zorbax Si, DuPont, Wilmington, DE). 40 mg enriched fraction B2, B3 or B4B dissolved in 1 ml chloroform/methanol/H_2O (60;40;9 v/v/v) was put on the column. A pump speed of 3 ml/min was used for pumping a total of 0.9 l solvent, collecting 300 fractions of 3 ml with a gradient of chloroform/methanol/H_2O (60;40;9 to 50;40;10 v/v/v). Fractions were analyzed on glass-backed HPLTC-plates as above. Purified fractions were pooled and evaporated to dryness in a rotary evaporator <30 °C, dessiccated and stored in <-20 °C. Approximately 20-25 rounds of this purification step was used i.e. using (20-25)x200 mg = 4-5 g Quil A starting material, including rechromatography to prepare 1 g of fraction B3. The yield of B2 and B4B was about 40% of the yield of B3.

The so prepared components B2, B3 and B4B were analyzed as follows.

a) Mass Spectrometry

Negative FAB-MS, Fig. 4, and positive FAB-MS (data not shown) were carried out for determination of molecular weights of the purified Quil A ocmponents B2, B3, B4A, and B4B. The data shown in Fig. 4 are

preliminary and will have to be re-acquired in a neutral pH matrix such as glycerol rather than in triethanolamine which was used for the spectra shown in Fig. 4. This is necessary because extreme alkali-lability of the compounds, pH > 8.5 have been demonstrated. Peaks at m/z 595, 744, and 893 stem from the matrix triethanolamine and should be disregarded. Our fraction B4A, which does not have any adjuvant or ISCOM particle forming capacity, seem to be identical with that described by Komori et al (for structure, see Fig. 10). The peaks corresponding to molecular weights of the three thus far most interesting glycosides are at: m/z 1988, B2; m/z 2150, B3; and m/z 1862, B4B.

b) ^{13}C-NMR

Fig.:s 5 and 6 show two regions, aliphatic carbon (8-45 ppm) and anomeric carbon (90-115 ppm), respectively, of the ^{13}C-NMR spectra for the full size fractions: A, B2 (20 mg); B, B3 (80 mg); and C, B4B (40 mg). All spectra were obtained in the solvent-system, chloroform/methanol/water (30:60:8, v/v/v). The triterpenoid region is well resolved (8-45 ppm, Fig. 6) and has been partially assigned as seen in Table 4.

TABLE 4

Partial ^{13}C-NMR signal assignment (ppm) for β-amyrin five-ring segment of fractions B2, B3, and B4B (see Fig. 5) obtained in chloroform/methanol/water (30:60:8, v/v/v).

Carbon#	B2	B3	B4B	Reference
C9[a]	-b	-b	-b	45.5
C10	36.4	36.2	36.3	37.0
C12	122.5	122.2	122.5	123.1
C13	144.1	146.6	143.6	144.8
C14	41.5	41.8	41.9	41.6
C15	30.0	30.5	30.7	30.7
C18	43.0	42.8	41.9	42.7
C20	30.7	30.6	30.6	30.7
C25	16.0	16.1	16.0	15.9
C26	17.7	17.3	17.6	17.6
C29	32.9	32.9	32.9	32.2

[a] Numbered as in Fig. 5.
[b] Hidden under methanol signal of solvent (confirmed with a DEPT experiment).

These assignments have been performed from studying a large number of reference-spectra obtained in various solvents and by analyzing the signals that are solvent-independent by a statistical comparison (data not shown). Fig. 6 shows the region between 80-148 ppm in the spectra of the three compounds, A, B2; B, B3; and C, B4B, featuring two double-bond carbon signals at 122 and 143 ppm corresponding to C-12 and C-13, respectively, in the β-amyrin skeleton (Fig. 10). The anomeric-carbon region, between 90-115 ppm, shows the presence of approximately 9-10 signals corresponding to the same amount of sugar-residues in the compounds.

Conclusion: Structural differences can be identified between fractions: A, B2; B, B3; and C, B4B, in both spectral regions corresponding to mainly the triterpenoid region and the oligosaccharide portions of the molecules, respectively. The exact amounts of sugars can not be determined at this point.

c) ^{1}H NMR

Fig. 11 demonstrates the full proton spectrum (0-10 ppm) and Fig. 12 partial proton spectrum (anomeric region, 4.0-6.0 ppm), respectively, of fractions: A, B2; B, B3; and C, B4B. The spectra are obtained from samples (≈ 10 mg, ≈ 600 scans) dissolved in DMSO.d_6/D_2O (98:2, v/v). To the far left in the spectrum (Fig. 11), at 9.4 ppm, the signal from the aldehyde proton on carbon-24 (see Fig. 5) is found. The doublet nature of this peak, a peak which is supposed to be a singlet, since it has no neighbouring protons to couple to, offers an explanation to the unusually complex anomeric region which is poorly resolved (as seen in the expansion in Fig. 12).

The doublet can be due to an aldehyde proton in two different compounds or to the presence of chemical exchange between two different populations of the same molecule (this process is slow enough in

NMR time scale to be observed) thus explaining the different integrals of the peaks in the doublet at different temperatures as shown in Fig. 13 and Table 5.

Table 5

Temperature in Degree K	Shift 1	Shift 2	Difference in Shifts	Integral Quote Shift 1/Shift 2
301	9.46	9.44	0.02	1.61
351	9.47	9.46	0.01	1.99
361	9.48	9.47	0.01	2.23

Fig. 13 and Table 5 (above) demonstrate that the relative integral of the peaks varies with temperature and that the two peaks move closer to each other at a higher temperature, both indicating that it can not be two different molecules but rather two different populations of the same molecule. This would explain the complex anomeric region by suggesting that many anomeric protons in the molecule would have double resonances due to different chemical environments in the two populations. However, the present set of data indicates that differences in the glycosylation of the compounds could provide part of the explanation of their structural differences (Fig. 12), by demonstrating different amount of anomeric proton signals in the spectra. The FAB-MS data for fractions B2, B3 and B4B also does not rule out the formal possibility that two similar size molecules, with very similar physico-chemical properties, exist that have the same amount of sugars but differ in linkage-positions and/or sequence.

Conclusion: In general, 1-dimensional ^1H NMR spectra from 8-10 sugar containing earlier unknown molecules are not sufficient for assignment of protons and detailed structural characterization. For resolving all signals and for making proper assignments through out the compounds it will be necessary to use the 2-dimensional NMR technique as well as chemically degrade the compounds for analysis. Both homonuclear (^1H-^1H) and heteronuclear (^1H-^{13}H) COSY, TOCSY as well as NOESY. The 2-dimensional proton phase sensitive correlation double quantum filtered NMR spectrum (DQFPSCOSY) for fraction B3 is shown in Fig. 14.

d) Summary of Structural Data

The conclusion of data generated thus far is that the active fractions that have adjuvant activity and ISCOM particle forming capacity in Quil A contain unique glycosylated triterpenoid-saponins that differ between each other in both their triterpenoid and glycan parts. They have an approximate structure like the one described in Fig. 10 and consist of a five-ring steroid skeleton of β-amyrin type and contains 8-11 sugar residues.

Example 7

0.1 mg cholesterol was mixed with ^3H-cholesterol (10 mg/ml dissolved in 20% MEGA-10 in H_2O) and 0.5 mg B2 or B3 or B4B or mixtures thereof. The volume was adjusted to 0.5 ml and the mixture dialysed against PBS on a preparation treated with ammonium molybdate (negative colouring technique). The dialysed preparations were analysed for the presence of complex with iscom structure by electron microscopy (EM) and analytical gradient centrifugation. In EM the iscom structure is characterized by a cage-like particle with a diameter of 40 nm composed of subunits with annular structure with a diameter of 12 nm. For sedimentation studies the sample is placed over a sacharose gradient (10-50%) and centrifuged for 18 hours, +10°C in a TST 41,14 rotor, 40 000 rpm. The gradient is collected in 18 fractions (fraction 1 = the bottom and fraction 18 = the top). By localizing the ^3H-cholesterol activity in the gradient, one can tell the sedimentation constant and see if complexes have been made.

B4B forms typical iscom structures with cholesterol but has no potent adjuvant activity.

B2 does not form iscom-like structures with cholesterol but binds to cholesterol. Together with B4B, B2 forms iscom-like structures with cholesterol. B2 has a weak adjuvant activity.

B3 binds to cholesterol but not in iscom-like structures. With B4B, B3 like B2, can form iscom-like structures with cholesterol. B3 has adjuvant activity.

Claims

1. Iscom matrix without any intentional antigens or antigenic determinants, comprising at least one lipid and at least one saponin for use as an immunomodulating agent.

2. Iscom matrix according to Claim 1, comprising at least one lipid, at least one saponin and at least one adjuvant.

3. Iscom matrix according to Claim 2, comprising a sterol, preferably cholesterol, one or more saponins, one or more adjuvants and one or more further lipids.

4. Iscom matrix according to any one of Claims 1-3, characterized in that the saponin is a triterpen-saponin, especially Quil A or one or more components thereof.

5. Iscom matrix according to Claims 1-4, comprising one or more immunomodulating compounds.

6. Iscom matrix according to any one of Claims 1-5, characterized in that it has an open spherical structure consisting of circular sub-units or parts of the spherical structure under electron microscopy and a sedimentation constant of about 12-22 S.

7. Iscom matrix according to Claims 1-6, characterized in that the saponin(s) is (are) derived form Quillaja Saponaria Molina of Beta Amyrin type with 8-11 carbohydrate moieties which have the following characteristics:
   a) Substance B2 has a molecular weight of 1988, a carbon 13 nuclear magnetic resonance (NMR) spectrum as indicated on Fig.:s 5A and 6A and a proton NMR spectrum as shown in Fig.:s 11A and 12A;
   b) Substance B3 has a molecular weight of 2150 and has a carbon 13 NMR spectrum as shown in Fig.:s 5B and 6B, and a proton NMR spectrum as shown in Fig.:s 11B and 12B;
   c) Substance B4B has a molecular weight of 1862, a carbon 13 NMR spectrum as shown in Fig.:s 5C and 6C, and a proton NMR structure as shown in Fig.:s 11C and 12C.

Patentansprüche

1. Iscommatrix ohne irgendwelche zweckbestimmten Antigene oder Antigendeterminanten, umfassend mindestens ein Lipid und mindestens ein Saponin zur Verwendung als Immunmodulierungsmittel.

2. Iscommatrix nach Anspruch 1, umfassend mindestens ein Lipid, mindestens ein Saponin und mindestens einen Hilfsstoff.

3. Iscommatrix nach Anspruch 2, umfassend ein Sterin, vorzugsweise Cholesterin, ein oder mehrere Saponin(e), einen oder mehrere Hilfsstoff(e) und ein oder mehrere weitere(s) Lipid(e).

4. Iscommatrix nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß das Saponin aus einem Triterpensaponin, insbesondere Quil A oder einer oder mehreren Komponente(n) hiervon, besteht.

5. Iscommatrix nach einem der Ansprüche 1 bis 4, umfassend eine oder mehrere immunmodulierende Verbindung(en).

6. Iscommatrix nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß sie unter dem Elektronenmikroskop eine offene kugelförmige Struktur aus zirkulären Untereinheiten oder Teilen der kugelförmigen Struktur und eine Sedimentationskonstante von etwa 12 - 22 S aufweist.

7. Iscommatrix nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das (die) Saponin(e) von Quillaja Saponaria Molina vom Beta-Amyrintyp mit 8 - 11 Kohlenhydrateinheiten der folgenden Eigenschaften:
   a) Substanz B2 weist ein Molekulargewicht von 1988, ein in den Fig. 5A und 6A dargestelltes ^{13}C-Kernresonanz (NMR)-Spektrum und ein in den Fig. 11A und 12A dargestelltes Protonen-NMR-Spektrum auf;

c) Substanz B3 weist ein Molekulargewicht von 2150, ein in den Fig. 5B und 6B dargestelltes ^{13}C-NMR-Spektrum und ein in den Fig. 11B und 12B dargestelltes Protonen-NMR-Spektrum auf;
c) Substanz B4B weist ein Molekulargewicht von 1862, ein in den Fig. 5C und 6C dargestelltes ^{13}C-NMR-Spektrum und ein in den Fig. 11C und 12C dargestelltes Protonen-NMR-Spektrum auf;
abgeleitet ist (sind).

Revendications

1. Matrice iscom dépourvue d'antigènes intentionnels ou de déterminants antigéniques, comprenant au moins un lipide et au moins une saponine pour son utilisation en tant qu'agent immunomodulateur.

2. Matrice iscom selon la revendication 1, comprenant au moins un lipide, au moins une saponine et au moins un adjuvant.

3. Matrice iscom selon la revendication 2, comprenant un stérol, de préférence le cholestérol, une ou plusieurs saponines, un ou plusieurs adjuvants et un ou plusieurs autres lipides.

4. Matrice iscom selon l'une quelconque des revendications 1 à 3, caractérisée en ce que la saponine est une saponine triterpénique, en particulier la Quil A ou un ou plusieurs de ses composants.

5. Matrice iscom selon les revendications 1 à 5, comprenant un ou plusieurs composés immunomodulateurs.

6. Matrice iscom selon une quelconque des revendications 1 à 5, caractérisée en ce qu'elle présente, à la microscopie électronique, une structure sphérique ouverte comprenant des sous-unités circulaires ou des parties de structure sphérique, et en ce qu'elle a une constante de sédimentation d'environ 12 à 22 S.

7. Matrice iscom selon les revendications 1 à 6, caractérisée en ce que la ou les saponines sont obtenues à partir de Quillaja Saponaria Molina et sont du type béta-amyrine avec de 8 à 11 fragments hydrates de carbone et qu'elles ont les caractéristiques suivantes :
a) la substance B2 a une masse moléculaire de 1988, un spectre de résonance magnétique nucléaire (RMN) du carbone 13 comme indiqué dans les figures 5A et 6A et un spectre de RMN du proton comme indiqué dans les figures 11A et 12A ;
b) la substance B3 a une masse moléculaire de 2150, un spectre de résonance magnétique nucléaire (RMN) du carbone 13 comme indiqué dans les figures 5B et 6B et un spectre de RMN du proton comme indiqué dans les figures 11B et 12B ;
c) la substance B4B a une masse moléculaire de 1862, un spectre de résonance magnétique nucléaire (RMN) du carbone 13 comme indiqué dans les figures 5C et 6C et un spectre de RMN du proton comme indiqué dans les figures 11C et 12C.

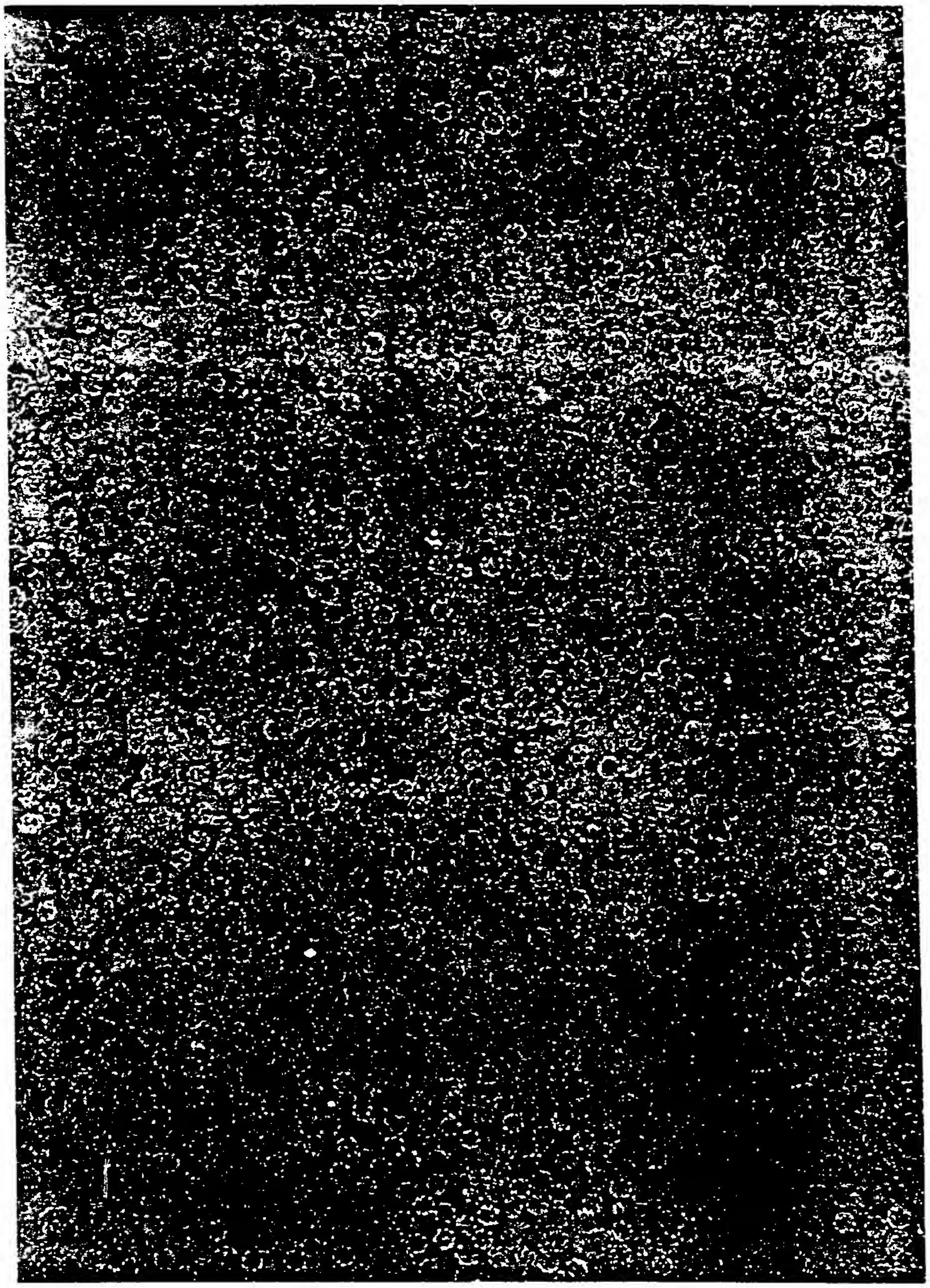

FIG. 1

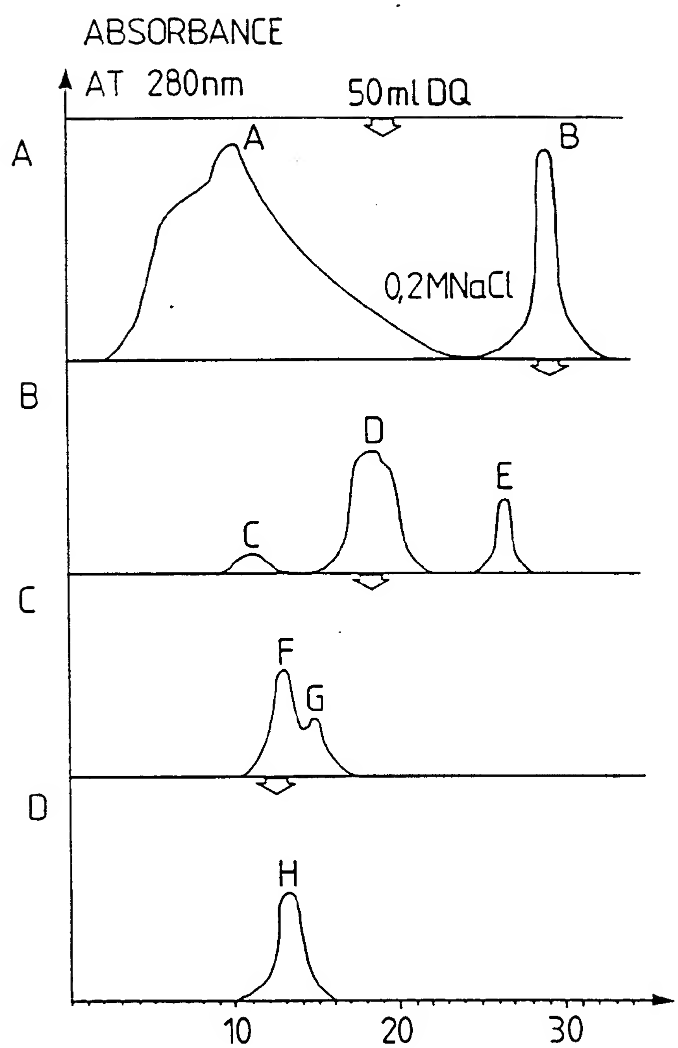

FIG.2

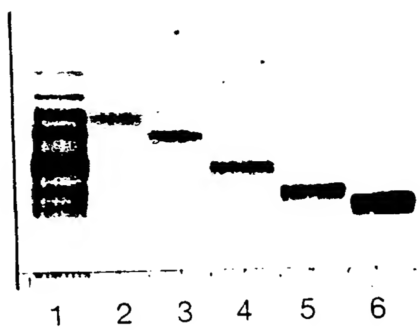

FIG. 3

FAB-SPECTRA

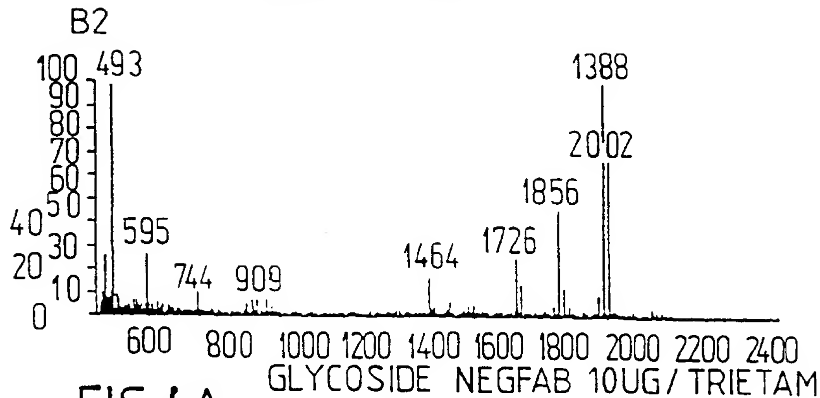

FIG.4A

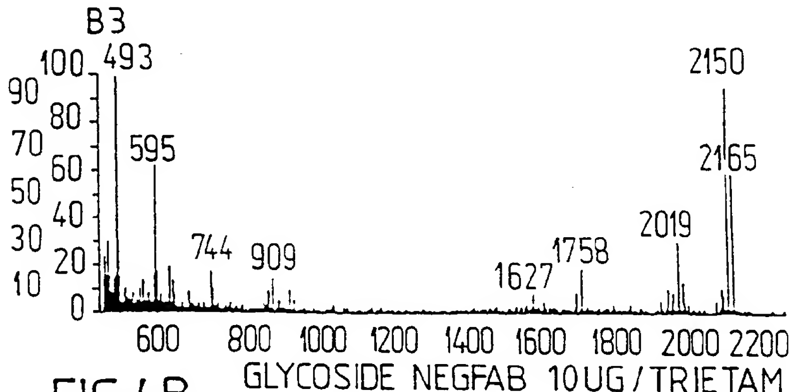

FIG.4B

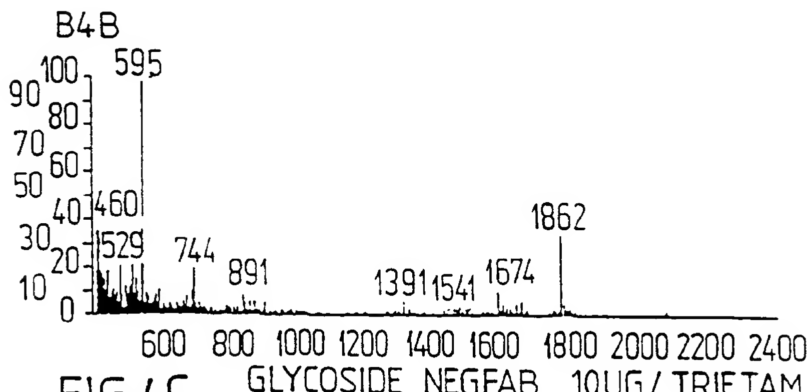

FIG.4C

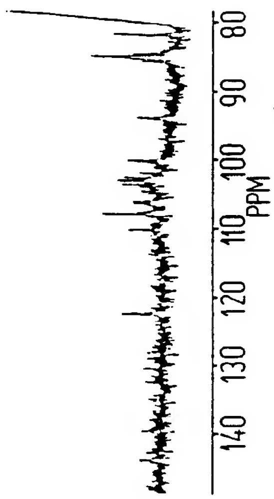

FIG.6A

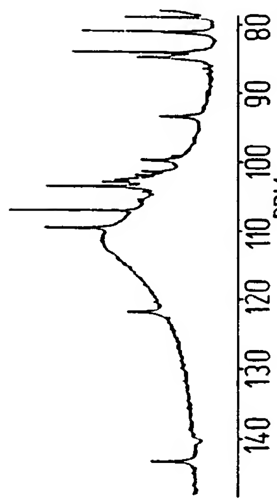

FIG.6B

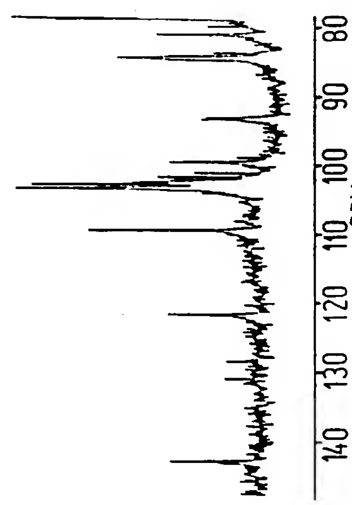

FIG.6C

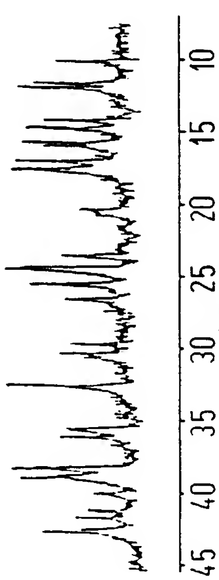

FIG.5A

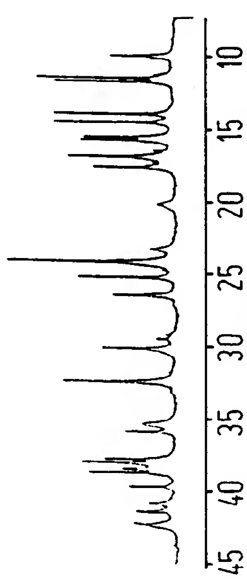

FIG.5B

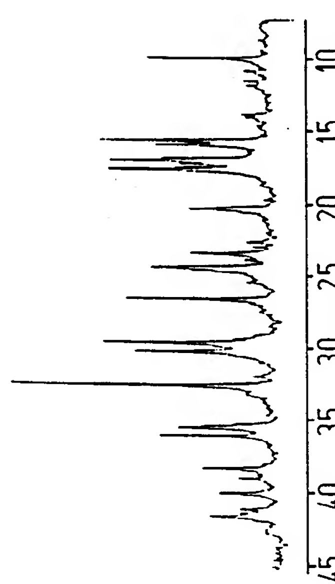

FIG.5C

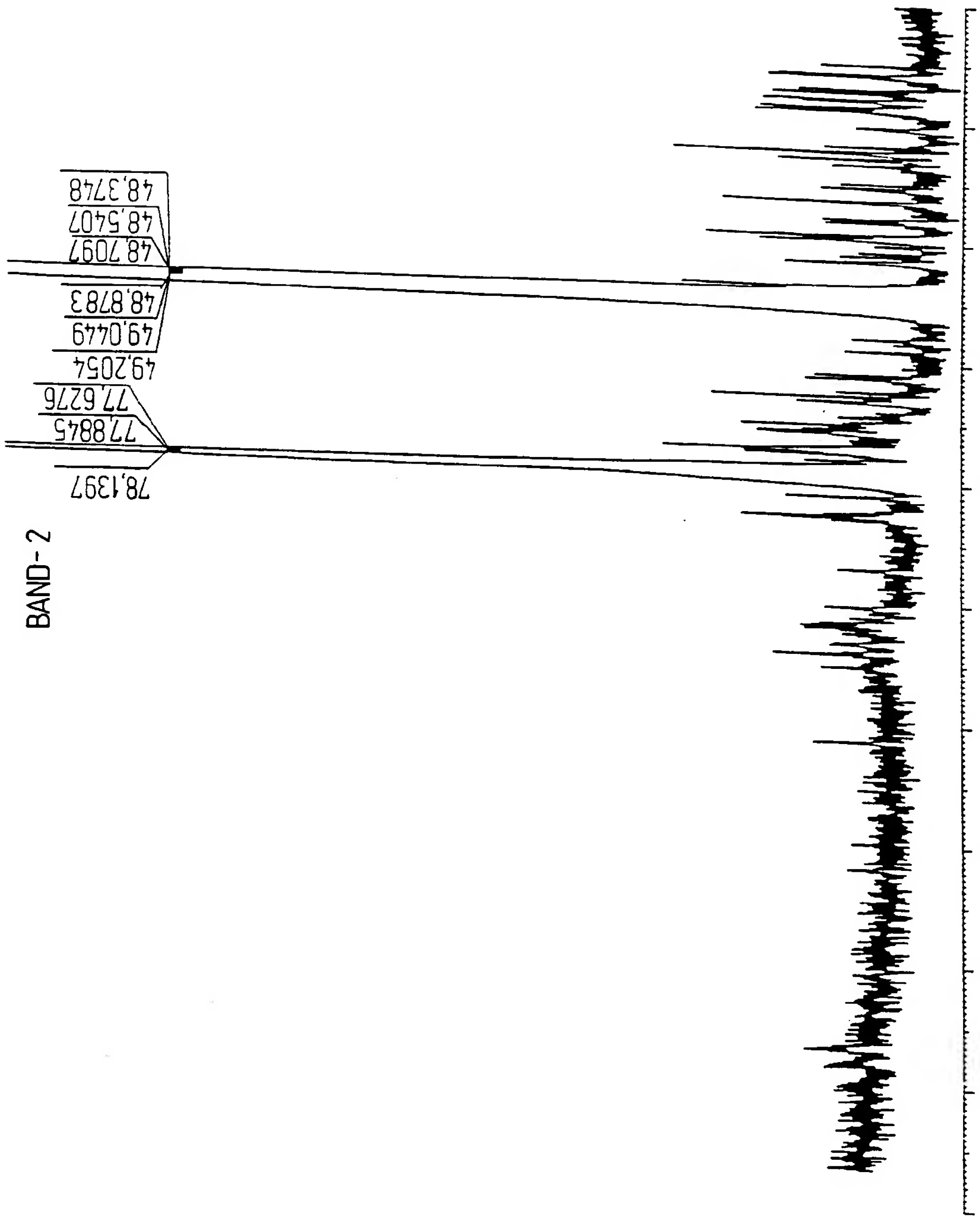
BAND-2
48,3748
48,5407
48,7097
48,8783
49,0449
49,2054
77,6276
77,8845
78,1397
20
40
60
80
100
PPM
120
140
160
180

FIG. 7

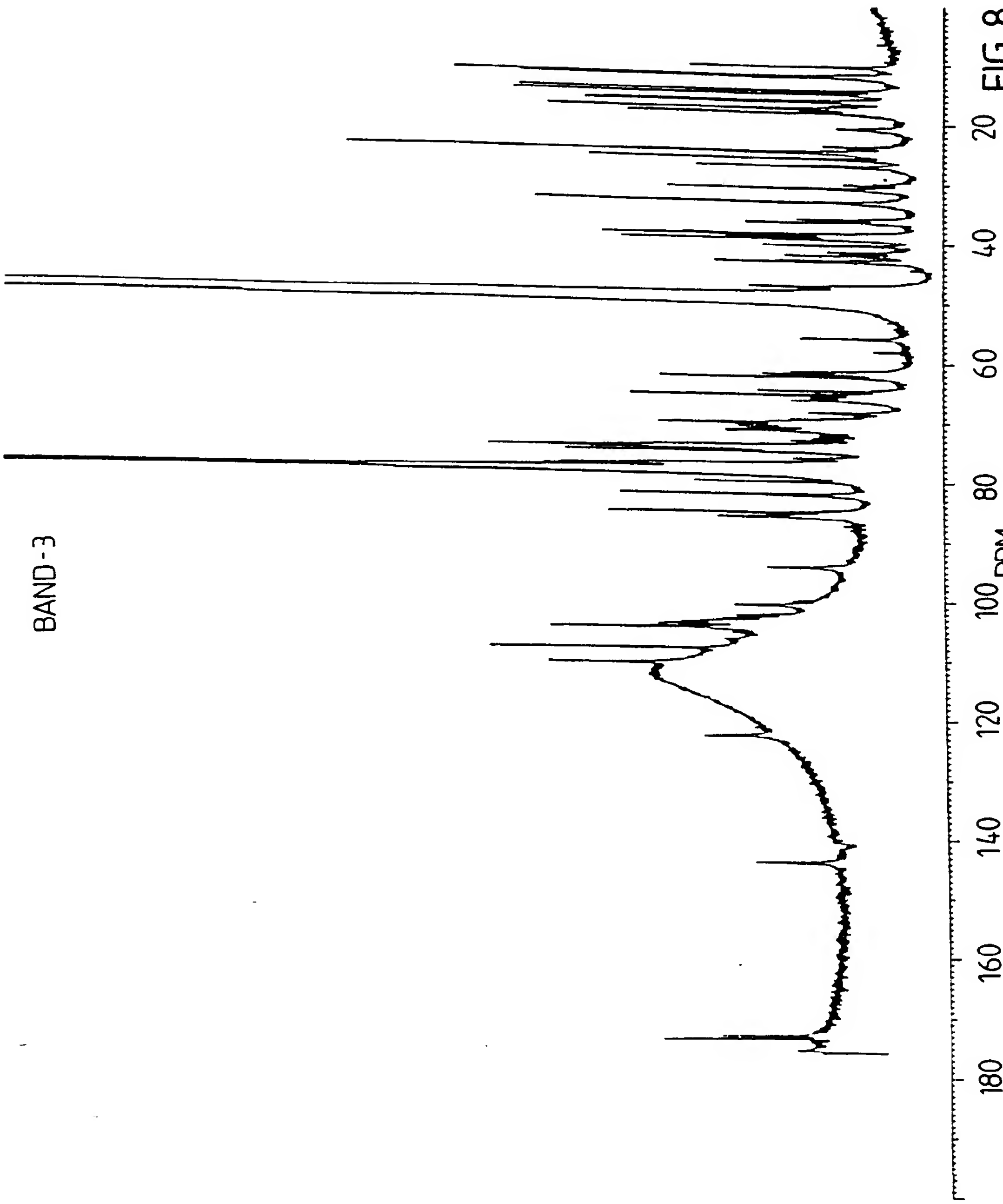

FIG. 8

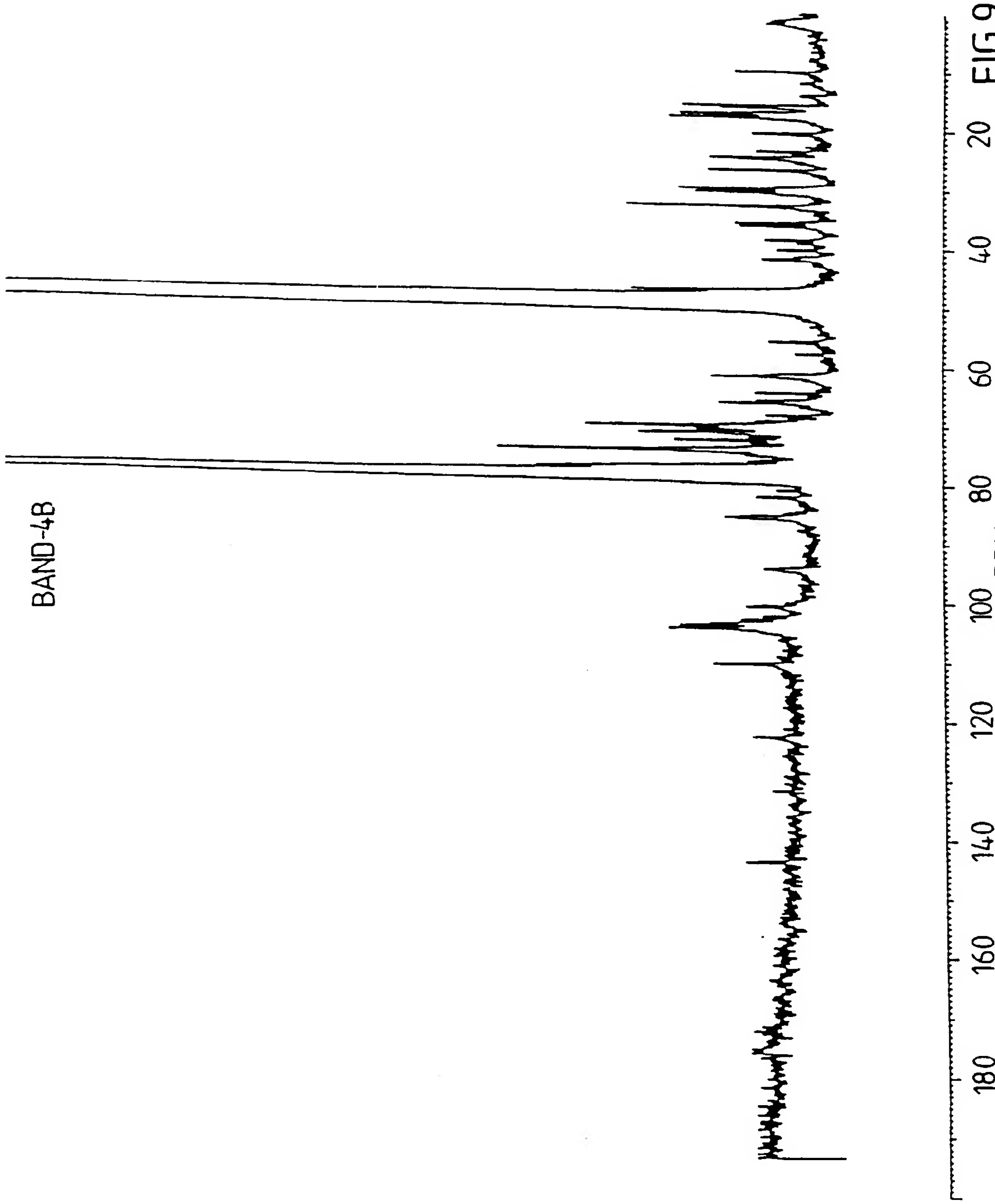

FIG.9

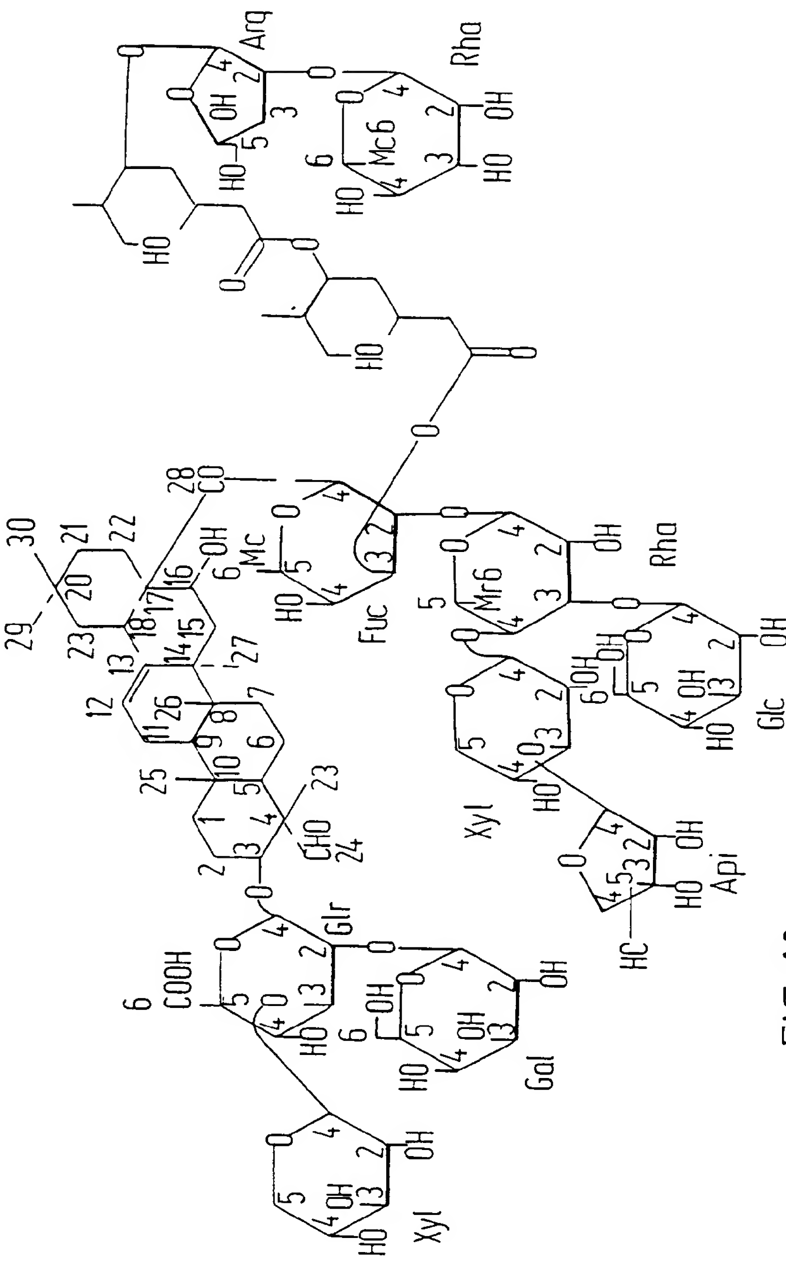

FIG. 10

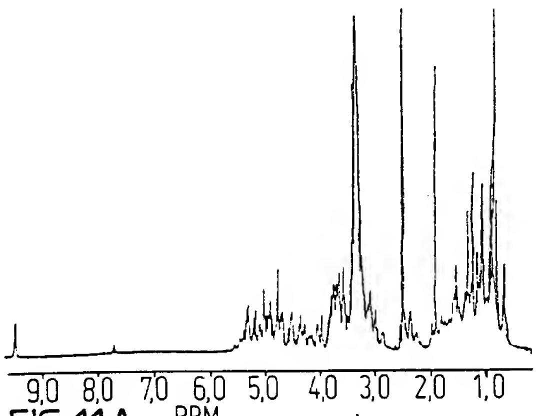

FIG.11A

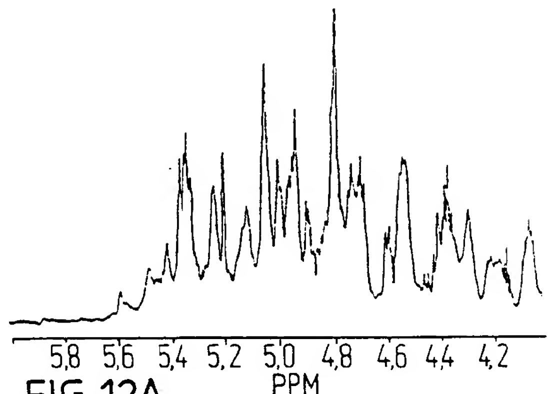

FIG.12A

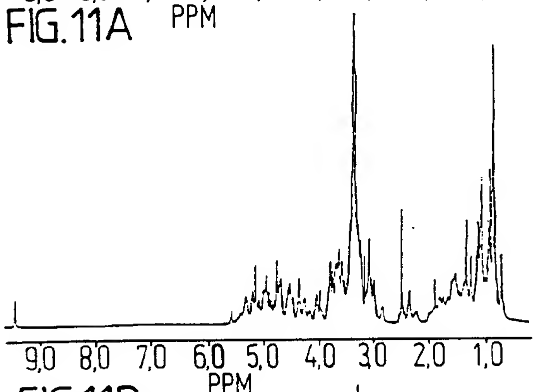

FIG.11B

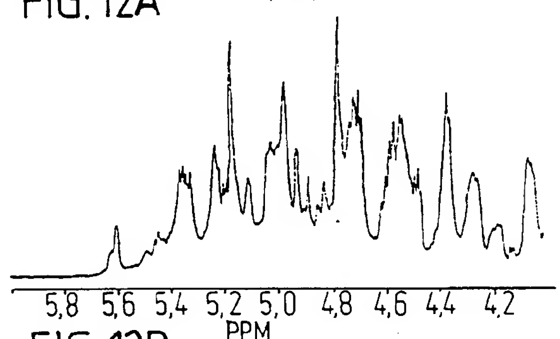

FIG.12B

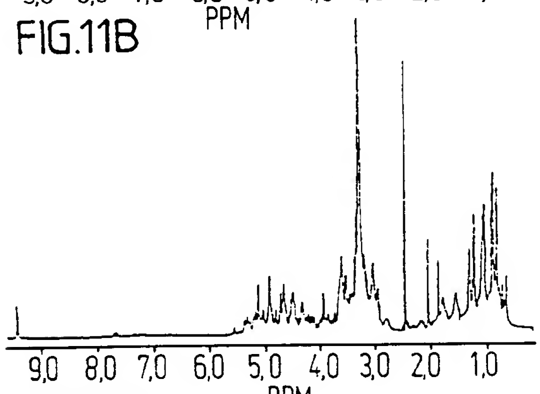

FIG.11C

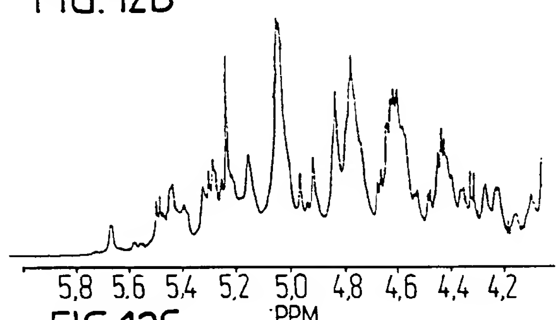

FIG.12C

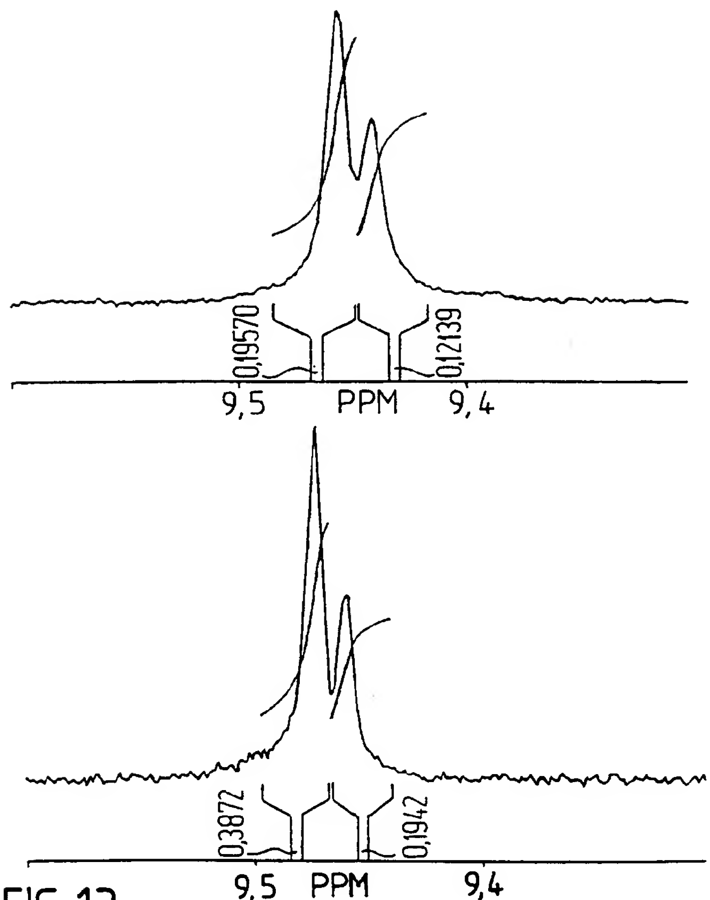
0,19570
0,12139
9,5
PPM
9,4
0,3872
0,1942
9,5
PPM
9,4

FIG. 13

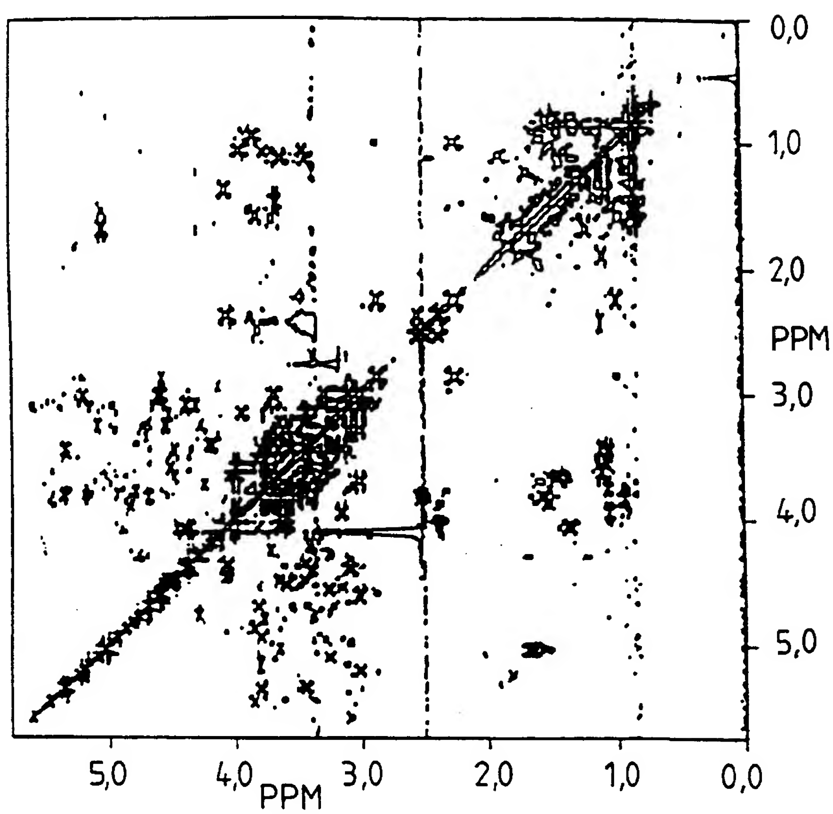
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FIG.14

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(54) **Stabilizer for 4-ethyl-2-hydroxyimino5-nitro-3-hexenamide-containing preparation, stabilizing method therefor and drug stabilized thereby.**

(57) A stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I) or a salt thereof acceptable as drug or drug containing as pharmacologically active ingredient a compound represented by a chemical formula (I) , in particular, (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or salt/s thereof acceptable as drugs, a stabilizing method by the use thereof and drugs containing such stabilizer and stabilized thereby.

$$
\begin{array}{ccccccc}
 & & & & NOH & & \\
 & & & & \| & & \\
CH_3-CH & - & C=CH- & & C & -CONH_2 & \qquad \ldots (I) \\
| & & | & & & & \\
NO_2 & & CH_2CH_3 & & & &
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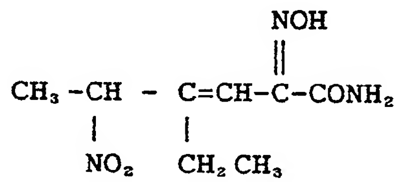
EP 0 452 697 A1

Rank Xerox (UK) Business Services

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I), in particular, (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or a saltt hereof acceptable as drug or drugs containing as pharmacologically active ingredient the obove compound, a stabilizing method by the use thereof and drugs containing such stabilizer and stab ilized thereby.



... (I)

Description of the Prior Art

It is well know from Japanese Laid-open Patent Publication No. 59-152366 that (E)-4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide or its salt/s accepted as drug has pharmacological activity as a vasodilating drug, anti-thrombotic drug, drug for angina pectoris or the like and, it is disclosed in the aforementioned publication that this compound can be manufactured as drugs in form of tablet, capsule, pellet, suppository and the like and that various excipients can be used in the manufacture thereof. Through further studies it has been confirmed that the aforementioned compound, in particular, (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide or a salt has a excellent pharmacological activity. Since this compound is called FK409 by this applicant and about it clinical studies are now under way, the compound to be stabilized by the method of the present invention will hereinafter be represented by this name.

SUMMARY OF THE INVENTION

FK409 is poor in stability and when, for instance, it is left standing at 40 °C for 2 months, it is completely decomposed to a dark brown fused substance with its pharmacological activity lost. For manufacture of drugs in some of the aforementioned forms it has to be mixed with proper excipients but when mixed with an excipient, it is extremely poor in stability and the content of the active ingredient is markedly reduced when it is left standing for 1 month at 40 °C.

The present invention has been made for improvement in this respect and is aimed at provision of a stabilizer effective for preventing decomposition of FK409 and having its pharmacological activity kept for a long period. Another object of the present invention is provision of a method of stabilizing FK409 or drugs containing it as the pharmacologically active ingredient. Still another object of the present invention is to provide a stabilized FK409 or drugs containing it as the pharmacologically activie ingredient.

DETAILED DESCRIPTION OF THE INVENTION

The stabilizer of the present invention is characterized in that it comprises one or more of group of polybasic acids, fatty acids with a carbon number of 16-20, ascorbic acid, erythorbic acid and riboflavin and the method of the invention is characterized in that stabilization is attained by mixing the aforementioned stabilizer in drugs containing FK409, and the stability of FK409 as a pharmacological ingredient is markedly improved and FK409-containing drugs excelled in durability of activity are obtained. The present inventors studied various compounds to see their stabilizing effect, that is, to see if they are effective for preventing decomposition of FK409, and as a result discovered that compounds selected from a group of polybasic acids, fatty acids 16-20 in carbon number, ascorbic acid, erythorbic acid and riboflavin have excellent stabilization effect. As polybasic acids may be cited dibasic acids such as tartaric acid, aspartic acid, succinic acid, malic acid, fumaric acid, maleic acid, malonic acid and gultaric acid, tribasic acid such as citric acid or anhydrides thereof. When the above exemplified polycarboxylic acid has an asymmetric carbon atom(s) such as tartaric acid, malonic acid or citric acid, each of D-form, L-form or racemic mixture

may be used.

As fatty acids 16-20 in carbon number may be cited saturated fatty acids such as palmitic acid, heptadecynoic acid, stearic acid, nonadecanoic acid and arachic acid, and unsaturated fatty acids such as undecylic acid, oleic acid and elaidic acid. Of these, particularly excelled in stabilization effect are oxydicaboxylic acids such as tartaric acid and their anhydrides, stearic acid as a saturated fatty acid with a carbon number of 18 in the group of fatty acids 16-20 in carbon number, ascorbic acid (vitamin C), erythorbic acid, riboflavin (Vitamin B2), etc. The salt of FK409 may be pharmaceutically acceptable salt including organic or inorganic salt.

As to the quantity of the aforementioned compound to be added as stabilizer, there is no limitation but it is preferred to be not less than 0.1 weight %, more preferably in a range of 0.3-5 weight %, of the quantity of FK409.

The drug composition of the present invention can be mixed with organic or inorganic carriers or excipients suited for external, oral or non-oral administration so as to be usable as solid, semisolid or liquid medical preparations containing the effective substance of the invention. The invented effective substance (ingredient) may be mixed with any of the ordinary, nontoxic carriers permitted for medical use and suited for preparation of tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions and the like. As such carriers may be cited water, dextrose, lactose, gum arabic, gelatin, mannitol, starch paste, magnesium silicate, talc, corn starch, keratin, colloid silica, potato starch and urea in solid, semisolid or liquid form, being suited for drug manufacture, and auxiliaries, stabilizers, thickeners, colorants and aromatics are also usable. It is also possible to use preservatives or bacteriostats for stably maintaining the activity of the drug or its effective ingredient in any given form. The medical composition of the invention is also usable for manufacture of persistent drugs of various forms. It is also possible to use the aforementioned drugs as long lasting drugs of various forms.

FK409 is poor in stability when mixed with an excipient for drug manufacture and its activity is lost quickly when the mixture is kept in stock at a high temperature, but its decomposition is markedly prevented when one of the aforementioned compounds is added as stabilizer for the resultant preparation or drug to be highly improved in durability of pharmacological activity.

The FK409 content of a drug of the present invention may be determined properly with the stage of the disease the drug is prescribed for and its form, if the desired therapeutic effect could be attained.

In applying the drug of the invention to human being, it may be prepared in various forms suited for venous or muscular injection, cutaneous administration as in the case of plaster or suppository or oral administration. The dosage depends on the stage of disease and the age of the patient but, generally, the effective dose of FK409 is approx. 0.1-100 mg/kg a day and normal per-time dose is 10 mg, 50 mg, 100 mg or 250 mg on the average.

Example

The composition and effect of the drug of the present invention will be specifically described below with reference to the cited example, but it is to be understood that this invention is not limited to the example described below.

First the stability of of FK409 when it was kept in a capsule, when it was stored mixed with an excipient and when it was mixed with tartaric acid as stabilizer (the residual percentage of FK409) was studied. In the experiment, however, the individual samples were put in #1 bottles, the filled bottles were then sealed, kept at the predetermined temperature and upon lapse of the predetermined time, the residual percentage of FK409 was measured by the liquid chromatographic method and its proportion to the initial content was determined.

The compositions of the individual samples are shown in Table 1 and the results in Table 2.

Table 1

	Recipe No.	1	2	3	4
Composition (mg)	FK409	3	3	3	3
	Lactose	-	87	84	-
	D-Mannit	-	-	-	84
	DL-Tartaric acid	-	-	3	3
	Total	3	90	90	90

Table 2

			Residual percentage (%)			
			Recipe 1	Recipe 2	Recipe 3	Recipe 4
original powder of FK409			100	100	100	100
Storage condition	40℃	1 month	0	0	95.3	98.6
		3 months	-	-	82.4	99.1
	Room temp.	6 months	0	0	96.1	100

As seen from Tables 1 and 2, FK409, either in the form of original powder (recipe No. 1) or mixed with an excipient (recipe No.2), totally loses its pharmacological activity after storage for 1 month at 40 °C , but when a proper dose of tartaric acid is added (as stabilizer), decomposition of FK409 is markedly prevented and its residual percentage is largely increased.

Table 3 below is given to show the result of study about various compounds on their stabilizing effect on the original powder of FK409.

Table 3

	Stabilizer dose(g)	Storage condition and residual (%)			
		40 ℃	50 ℃	60℃	60℃
		1 month	1 month	18 days	7 days
FK409					
Original powder	-	0	0	0	99.3
DL-Tartaric acid	1	97.2	98.0	88.1	99.0
Stearic acid	1	99.3	95.2	-	-
Vitamin C	1	97.1	98.3	87.8	99.0
Erythorbic acid	1	96.3	98.4	83.5	99.8
Vitamin B2	1	97.3	93.9	-	96.0
DL-Malonic acid	1	98.9	83.5	32.5	90.1
DL-citric acid anhydride	1	70.1	76.3	-	-

The dose of stabilizer in g is per 1 g of the original powder of FK409.

As is apparent from Table 3, the compounds used in this experiment all have excellent stabilizing effect on FK409, DL-tartaric acid, stearic acid, vitamin C and erythorbic acid in particular.

The storage conditions in this experiment are rather severe ones, one month of storage at 50°C being equivalent to storage at the room temperature for approx. 12 months and, this taken into consideration, the effect of this invention is truly outstanding.

Then, the stabilizing effect of tartaric acid on tablets with FK409 as active ingredient will be demonstrated.

The ingredients in the recipe shown Table 4 except only magnesium stearate were mixed, 40 ml of water was added to the mixture (approx. 135 g) and the wetted mixture was uniformly kneaded, vacuum dried and granulated. To the granules the prescribed amount of magnesium stearate was added and, after mixing, the mixture was made into tablets 7mm in diameter by the use of a tablet making machine.

40 tablets thus obtained were put in a #3 bottle, the filled sealed bottle was stored for the predetermined period at the room temperature (25°C) or 40 °C , and then the residual percentage of FK409 was studied.

The result was as shown in Table 5, and from the tabulated data it is apparent that tartaric acid has an excellent stabilizing effect on FK409 even when it is prepared in tablet form.

Table 4

Recipe No.		1	2	3	4
Compo-sition (mg)	FK409 (Pharma. ingredient)	10	40	10	40
	DL-Tartaric acid (stabilizer)	3	12	3	12
	D-Mannit	107.95	68.95	107.95	68.95
	ECG 505	12	12	-	-
	Ac-Di-Sol	-	-	12	12
	TC-5E	1.35	1.35	1.35	1.35
	Magnesium stearate	0.7	0.7	0.7	0.7
	Total	135	135	135	135

ECG 505: Carboxyl methyl cellulose calcium (disintegrator)

Ac-Di-Sol: Crosslinked-carboxyl methyl cellulose-sodium (disintegrator)

TC-5E: Hydroxy propyl methyl cellulose (binder)

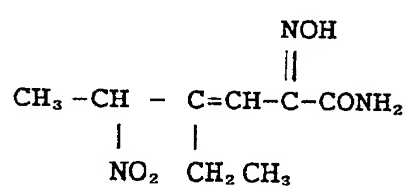
Magnesium stearate (lubricant)

Table 5

			Residual percentage (%)			
			Recipe 1	Recipe 2	Recipe 3	Recipe 4
Initial			100.0	100.0	100.0	100.0
Storage condition	40 ℃	1 month	98.9	100.0	99.9	100.0
		6 months	96.8	97.3	95.1	95.8
	Room temp.	1 month	100.0	99.9	99.3	100.0
		6 months	99.2	99.8	99.3	99.6

Claims

1. A stabilizer for 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide represented by the following chemical formula (I) or a salt thereof acceptable as drug or drug containing as pharmacologically active ingredient a compound represented by the chemical formula (I) or a salt thereof acceptable as drug, wherein said stabilizer is one or more selected from a group of polybasic acids, fatty acids 16-20 in carbon number, ascorbic acid, erythorbic acid and riboflavin.



... (I)

2. A stabilizer according to claim 1 wherein said 4-ethyl-2-hydroxyimino-5-nitro-3-hexenamide is (±)-(E)-4-ethyl-2-[(E)-hydroxyimino]-5-nitro-3-hexenamide.

3. A stabilizer according to claim 1 or 2, wherein said polybasic acid is oxydicarboxylic acid.

4. A stabilizer according to claim 3, wherein said oxydicarboxylic acid is tartaric acid.

5. A stabilizer according to claim 2, wherein said fatty acid 16-20 in carbon number is a saturated fatty acid.

6. A stabilizer according to claim 5, wherein said saturated fatty acid is stearic acid.

7. A stabilizing method for a compound represented by a chemical formula (I) or a salt thereof acceptable as drug, wherein said stabilizer mentioned in any one of claims 1-6 is mixed with a compound represented by said chemical formula (I) or a salt thereof accepted as drug.

8. A stabilizing method according to claim 7, wherein said stabilizer is tartaric acid.

9. A stabilizing method according to claim 7 or 8, wherein the quantity added of said stabilizer is not less than 0.1 weight part is mixed with 1 weight part of said compound represented by said chemical formula (I) or a salt thereof accepted as drug.

10. A stabilizing method according to claim 9, wherein the quantity added of said stabilizer is 0.3-5 weight part.

11. A stabilized drug, wherein a stabilizer mentioned in any one of claims 1-6 is mixed with a compound represented by said chemical formula (I) or a salt thereof accepted as drug.

12. A stabilized drug according to claim 11, wherein said stabilizer is tartaric acid.

13. A stabilized drug according to claim 11 or 12, wherein the quantity added of said stabilizer is not less than 0.1 weight part per 1 weight part of said compound represented by said chemical formula (I) or a salt thereof accepted as drug.

14. A stabilized drug according to claim 13, wherein the quantity added of said stabilizer is 0.3-5 weight parts.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 10 4502

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y,D	EP-A-0 113 106 (FUJISAWA PHARMACEUTICAL CO., LTD) * Page 1, lines 1-7; page 39, example 1; claims 7,8 * & JP-A-59 152 366	1-14	A 61 K 31/16 A 61 K 47/12 A 61 K 47/22
Y	PATENT ABSTRACTS OF JAPAN, vol. 9, no. 145 (C-287)[1868], 20th June 1985; & JP-A-60 028 923 (TEIJIN K.K.) 14-02-1985 * Abstract *	1-14	
Y	PATENT ABSTRACTS OF JAPAN, vol. 8, no. 150 (C-233)[1587], 12th July 1984; & JP-A-59 055 828 (NITTO DENKI KOGYO K.K.) 31-03-1984 * Abstract *	1	
Y	FR-A-2 333 494 (SENJU PHARMACEUTICAL CO., LTD) * page 1, lines 1-4; page 3, lines 2-13; pages 5,6, experience 1; claims 1-3 *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	04 July 91	BOULOIS D.J-M.

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
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- A: technological background
- O: non-written disclosure
- P: intermediate document
- T: theory or principle underlying the invention
- E: earlier patent document, but published on, or after the filing date
- D: document cited in the application
- L: document cited for other reasons
- &: member of the same patent family, corresponding document

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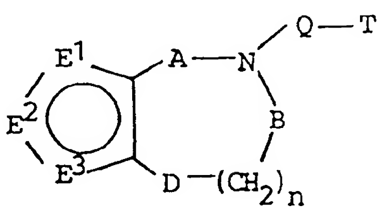
(54) **Fused thiophene compounds and uses thereof.**

(57) A fused thiophene compound of the formula :



(I)

or a pharmaceutically acceptable acid addition salt thereof. In the above formula, one of E^1, E^2 and E^3 is sulfur atom and other two of them are C-R^1 and C-R^2 respectively. R^1 and R^2 are the same or different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, arylalkyl, acyl, alkoxyalkyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, hydroxyalkanoyl, aryloxyalkanoyl, haloalkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, halosulfonyl, sulfamoyl, substituted sulfamoyl, carboxyl, acylamino, alkoxycarbonyl, carbamoyl, substituted carbamoyl or substituted amino. D is -CH_2- or -$S(0)_m$- (m is 0, 1 or 2). Q is straight or branched chain alkylene. T is primary amino, secondary amino or tertiary amino. A and B are the same or different and each is carbonyl or thiocarbonyl, or one of A and B is absent and the other of them is carbonyl or thiocarbonyl, or A is -CH_2- and B is carbonyl or thiocarbonyl, and n is 1, 2 or 3 with the proviso that n is 2 or 3 when one of A and B is absent and the other of them is carbonyl or thiocarbonyl, and n is 1 or 2 when A and B are other combinations. In the above definitions, (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents. Said compounds have selective affinity for 5-HT_{1A} receptor, or high affinity for 5-HT_{1A} and dopamine D_2 receptors so that they are useful as antianxietic drug, antipsychotic drug or drug for the disease of circulatory system. The intermediates for said fused thiophene compounds are also disclosed.

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The present invention relates to novel and pharmaceutically useful fused thiophene compounds, pharmaceutically acceptable acid addition salts thereof useful as medical agents for central nervous system and circulatory system, and pharmaceutical uses thereof, and further novel synthetic intermediates for said fused thiophene compounds.

The benzodiazepine compounds have been widely used as antianxietic agents. Though these compounds have potent anxiolytic action, they have side effects such as muscle-relaxation effect, sedative action, drug dependence and so on. Therefore, there are some problems that these agents must be cautiously applied to patients suffering from anxiety neurosis like psychosomatic disease in the daytime (usually called as daytime anxiety). Recently, the researches for compounds having non-benzodiazepine structure have been devoted to the development of antianxietic drugs which act selectively on anxiety. The representative of such compounds is buspirone (INN). Differing from hitherto benzodiazepine compounds, buspirone is known not to bind to benzodiazepine receptor but has high affinity for serotonin 1A receptor and exhibits antianxietic action by an interaction with serotonin 1A receptor. Since such new compounds have superior property such as high safety, less habit-forming and less probability of abuse, they are expected to be new prototype of antianxietic drugs. However, the problems to be solved still remain since they need long time to exhibit their activities and have side effects in extrapyramidal system.

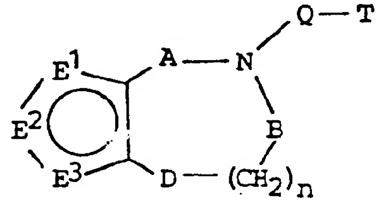
The existing antipsychotic drugs are effective on so called positive symptoms like hallucination, delusion or the like as well as on psychomotor excitement but not effective on negative symptoms like apathy, abulia, disorder of cognition and so on. Further, as unavoidable side effects such as acute dystonia, akathisia or Parkinsonism are observed at the initial stage of treatment with antipsychotic drugs and extrapyramidal syndromes like late dyskinesia are observed during the long term administration. Because of the limitation of the treatment with the existing antipsychotic drugs, the development of antipsychotic drugs which are effective on negative symptoms and with reduced side effects has been expected. From this point of view, it is desired to develop new antipsychotic drugs which have affinity for both serotonin and dopamine receptors, and especially bind more selectively to serotonin receptor.

Recently a relationship between serotonin 1A receptor and hypotensive action has been reported. That is, it is known that 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) which has high affinity for serotonin 1A receptor lowers blood pressure through serotonin 1A receptor of medulla oblongata. In accordance with this fact, the compounds having high affinity for serotonin 1A receptor can be developed as anti-hypertensive drug. This kind of compounds are expected to be useful antihypertensive drug because they do not cause rebound phenomenon, hyposalivation or sympatheticotonia (that is, bradycardic action rather than tachcardiac action). For example, it is known that piperazine derivatives are one of such drugs exhibiting hypotensive action by central action mechanism (U.S. Patent No. 4,833,142).

The present inventors have made intensive investigations in order to provide compounds having more potent and selective antianxietic action with less side effects than the existing compounds by selectively binding to serotonin 1A receptor. The present inventors have also investigated to find compounds having affinity for serotonin and dopamine receptors, especially more selective affinity for serotonin receptor which are useful as antipsychotic drugs, and further to find compounds useful as exellent antihypertensive drugs which interact with serotonin 1A receptors and does not increase heart rate.

As a result of such investigations, the present inventors have found novel fused thiophene compounds which accord with the above-mentioned purpose, and completed the present invention. The present invention provides novel fused thiophene compounds useful as anti-anxietic drug, antipsychotic drug or antihypertensive drug and novel synthetic intermediates for the fused thiophene compounds.

The present invention relates to a fused thiophene compound of the formula:



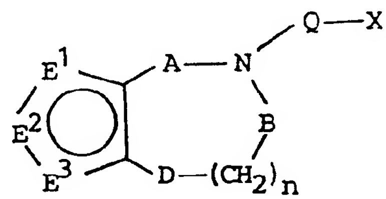
(I)

or a pharmaceutically acceptable acid addition salt thereof.

In the above formula, one of E^1, E^2 and E^3 is sulfur atom and other two of them are C-R^1 and C-R^2 respectively; R^1 and R^2 are the same or different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, arylalkyl, acyl, alkoxyalokyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyal-

kanoyl, hydroxyalkanoyl, aryloxyalkanoyl, haloalkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, halosulfonyl, sulfamoyl, substituted sulfamoyl, carboxyl, acylamino, alkoxycarbonyl, carbamoyl, substituted carbamoyl or substituted amino; D is $-CH_2-$ or $-S(O)_m-$ (m is 0, 1 or 2). Q is straight or branched chain alkylene. T is primary amino, secondary amino or tertiary amino. A and B are the same or different and each is carbonyl or thiocarbonyl, or one of A and B is absent and the other of them is carbonyl or thiocarbonyl, or A is $-CH_2-$ and B is carbony or thiocarbonyl, and n is 1, 2 or 3 with the provisos that n is 2 or 3 when one of A and B is absent and the other of them is carbonyl or thiocarbonyl, and n is 1 or 2 when A and B are other combinations. In the above definitions, (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents.

The present invention also provides a fused thiophene compound of the formula:



(II)

In the above formula, X is hydroxyl, reactive atom or group derived from hydroxyl (e.g. halogen, methanesulfonyloxy, or paratoluenesulfonyloxy), a group of $-CO-R^3$ (R^3 is hydrogen or alkyl), cyano, carbamoyl or nitro, and other symbols are as defined above.

In the present specification, the compounds of formula (II) can be subdivided into five groups of the compounds of formula (II-a) to (II-e) as follows:

A compound of formula (II-a): X is hydroxyl, or reactive atom or group derived from hydroxyl.

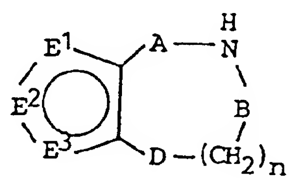
A compound of formula (II-b): X is $-CO-R^3$ (R^3 is hydrogen or alkyl).

A compound of formula (II-c): X is cyano.

A compound of formula (II-d): X is carbamoyl.

A compound of formula (II-e): X is nitro.

The present invention further provides a fused thiophene compound of the formula:



(IV)

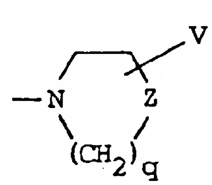
wherein each symbol is as defined above. The compounds of formula(I) and (IV) are synthetic intermediates of the compound of formula (I).

In the definitions of the above symbols and in the present specification, halogen means chlorine, bromine, fluorine, iodine; alkyl means, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, decyl, hexadecyl or octadecy; alkoxy means, for example, methoxy, ethoxy, propxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy or octyloxy; haloalkyl means alkyl substituted by halogen, for example, bromomethyl, chloromethyl, trifluoromethyl, 2-bromoethyl, 2-chloroethyl, difluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-bromopropyl, 3-chloropropyl or 4-fluorobutyl; arylalkyl means, for example, benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, naphthylmethyl, 2-naphthylethyl, 3-naphthylpropyl, 4-naphthylbutyl, diphenylmethyl or bis(4-fluorophenyl)methyl; acyl means, for example, alkanoyl such as acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl or octanoyl, aroyl such as benzoyl or naphthoyl, or heteroarylcarbonyl such as nicotinoyl, thenoyl or furoyl; alkoxyalkyl means, for example, methoxymethyl, 1- or 2-methoxyethyl, 1-, 2- or 3-methoxypropyl, 1-, 2-, 3- or 4-methoxybutyl, ethoxymethyl, 1- or 2-ethoxyethyl, 1-, 2- or 3-ethoxypropyl or 1-, 2-, 3-, or 4-ethoxybutyl; acyoxyalkyl means, for example, acetoxymethyl, propionyloxymethyl, 1- or 2-acetoxyethyl, 1- or 2-propionyloxyethyl, 1-, 2- or 3-acetoxypropyl, 1-, 2- or 3-propionyloxypropyl, benzoyloxymethyl, 1- or 2-benzoyloxyethyl, 1-, 2- or 3-benzoyloxypropyl or 1-, 2-, 3- or 4-benzoyloxybuty; hydroxyalkyl means, for example, hydroxymethyl, 1- or 2-hydroxyethyl, 1-, 2- or 3-hydroxypropyl or 1-, 2-, 3- or 4-hydroxybutyl; acyloxyalkanoyl means, for example, acetoxyacetyl, acetoxypropionyl, acetoxybutyryl, benzoyloxyacetyl, benzoyloxypropionyl or benzoyloxybutyryl; alkoxyalkanoyl means,

for example, methoxyacetyl, ethoxyacetyl, propoxyacetyl, butoxyacetyl, methoxypropionyl, ethoxypropionyl, propoxypropionyl or butoxypropionyl; hydroxyalkanoyl means, for example, hydroxyacetyl, hydroxypropionyl or hydroxybutyryl; aryloxyalkanoyl means, for example, phenoxyacetyl, phenoxypropionyl or phenoxybutyryl; haloalkanoyl means, for example, bromoacetyl, chloroacetyl, bromopropionyl, chloropropionyl, bromobutyryl or chlorobutyryl; alkylthio means, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio or tert-butylthio; alkylsulfonyl means, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl or tert-butylsulfonyl; halosulfonyl means, for example, chlorosulfonyl, bromosulfonyl or iodosulfonyl; substituted sulfamoyl means, for example, dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl, dibutylsulfamoyl, piperidinosulfonyl or morpholinosulfonyl; alkylsulfinyl means, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl or butylsulfinyl; arylthio means, for example, phenylthio or naphthylthio; arylsulfinyl means, for eaxmple, phenylsulfinyl or naphthylsulfinyl; arylsulfonyl means, for example, phenylsulfonyl or naphthylsulfonyl; acylamino means, for example, acetylamino, propionylamino, butyrylamino or benzoylamino; alkoxycarbonyl means, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl or isobutoxycarbonyl; substituted carbamoyl means, for example, dimethylcarbamoyl, diethylcarbamoyl or piperidinocarbonyl; substituted amino means, for example, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dipropylamino, N-methyl-N-benzylamino or piperidino; straight alkylene means, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene or decamethylene; branched alkylene means, for example, alkylene substituted by at least one, preferably 1 to 4 alkyl such as propylene, 1-methyltrimethylene, 3-methyltrimethylene, 1-methyltetramethylene, 4-methyltetramethylene, 1,4-dimethyltetramethylene, 6-methylhexamethylene or 4,4-dimethyltetramethylene.

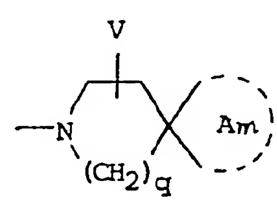
In the formula (I), T is primary amino of $-NH_2$, secondary amino of -NHRa wherein Ra is alkyl (same as the above), cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl), arylalkyl (same as the above) or heteroarylalkyl (which may optionally be reduced, e.g. pyridylmethyl, furylmethyl, thienylmethyl or (1,4-benzodioxan-2-yl)methyl), or tertiary amino of -N(Rb)(Rc) wherein Rb and Rc are the same or different and each is alkyl (same as the above), cycloalkyl (same as the above), arylalkyl (same as the above) or heteroarylalkyl (same as the above), and -N(Rb)(Rc) is examplified by dialkylamino (e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, dihexylamino, dioctylamino), N-alkyl-N-cycloalkylamino (e.g. N-methyl-N-cyclopropylamino, N-methyl-N-cyclohexylamino, N-methyl-N-cyclopentylamino, N-ethyl-N-cyclopropylamino, N-ethyl-N-cyclopentylamino, N-ethyl-N-cyclohexylamino, N-propyl-N-cyclopropylamino, N-propyl-N-cyclohexylamino, N-butyl-N-cyclohexylamino), N-alkyl-N-arylalkylamino (e.g. N-methyl-N-benzylamino, N-methyl-N-(2-phenylethyl)amino, N-methyl-N-(3-phenylpropyl)amino, N-ethyl-N-benzylamino, N-ethyl-N-(2-phenylethyl)-amino, N-propyl-N-benzylamino, N-propyl-N-(2-phenylethyl)amino, N-butyl-N-benzylamino, N-butyl-N-(2-phenylethyl)amino) or N-alkyl-N- heteroaryl amino (e.g. N-methyl-N-pyridylmethylamino, N-methyl-N-thienylmethylamino, N-methyl-N-furylmethylamino, N-ethyl-N-pyridylmethylamino,N-ethyl-N-thienylmethylamino, N-ethyl-N-furylmethyl-amino, N-methyl-N-(1,4-benzodioxan-2-ylmethyl) amino), or Rb and Rc together with the adjacent nitrogen atom form a cyclic amino of the formula:

(1)



or

(2)



wherein q is an integer of 1 to 4, Z is methylene, oxygen atom, sulfur atom or $N-R^5$. Substituent V is hydrogen, hydroxyl, amino, carbamoyl, mono or di-substituted amino (e.g. methylamino, dimethylamino, ethylamino, diethylamino, anilino, N-acetylanilino, N-propionylanilino or pyrrolidinylanilino), cyclic amino (e.g. pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, thiomorpholino, piperazinyl, homopiperazinyl, 4-substituted-piperazinyl or 4-substituted-homopiperazinyl), acyl (same as the above), aryl (e.g. phenyl, naphthyl), arylalkyl (same as the above), arylalkylamino (e.g. benzylamino, phenylethylamino, naphthylmethylamino or naphthylethylamino) alkyl (same as the above), alkoxy (same as the above), hydroxyalkyl (same as the above), alkoxy carbonyl (same as the above), heteroaryl (e.g. pyridyl, thienyl, furyl, pyrimidinyl, 1,2-benzoisothiazol-3-yl, 1,2-benzoisoxazol-3-yl, benzothiophen-3- or 4-yl, bezofuran-3- or 4-yl, quinolyl, isoquinolyl, benzoxazol-2-yl, pyrazinyl, piridazinyl, imidazolyl, thieno[3,2-c]pyridin-4-yl, furo[3,2-c]pyridin-4-yl, 2-oxo-1-benzimidazolyl, 2-thioxo-1-benzimidazolyl, 2,4-dioxohexahydro-pyrimidin-1-yl, hydantoin-1-yl), phenoxyalkyl (e.g. phenoxymethyl, 2-phenoxyethyl, 3-phenoxypropyl), anilinoalkyl (e.g. anilinomethyl, 2-anilinoethyl, 3-anilinopropyl),

alkylaminoalkyl (e.g. N-methylaminomethyl, N,N-dimethylaminomethyl, N,N-diethylaminomethyl, 2-(N-methylamino)ethyl, 2-(N,N-dimethylamino)ethyl), alkanoylaminoalkyl (e.g. N-acetylaminomethyl, N-propionylaminomethyl, N-butyrylaminomethyl, 2-(N-acetylamino)ethyl) or bisarylmethylene (e.g. bis(4-fluorophenyl)-methylene, bis(4-chlorophenyl)methylele) and the number of V is 1 to 4. R^5 of N-R^5 is hydrogen, alkyl (same as the above), cyanoalkyl (e.g. cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl), hydroxyalkyl (same as the above), aryl (same as the above), arylalkyl (same as the above), alkoxycarbonyl (same as the above), diarylalkyl (e.g. diphenylmethyl, bis(4-fluorophenyl)methyl, 2,2-diphenylethyl, 2,2-bis(4-fluorophenyl)ethyl), heteroaryl (same as the above), heteroarylalkyl (same as the above), cycloalkyl (same as the above), cycloalkylalkyl (e.g. cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, cycloheptylmethyl), acyl (same as the above), cinnamyl or adamantanemethyl. Cyclic amino of formula (1) may contain carbonyl group in the cycle and further may be fused with aryl (e.g. benzene, naphthalele) or heteroaryl (e.g. furan, thiophene, pyridine, quinoline) to form fused cyclic amino such as 1,2,3,4-tetrahydroisoquinolin-2-yl or phthalimido. Ring Am of formula (2) contain amido bond in the cycle and further may contain oxygen atom, sulfur atom, carbonyl and/or N-R^6 (R^6 is hydrogen, alkyl or phenyl). The ring Am having amido bond in the cycle includes, for example, thiazolidinone, imidazolidinone, pyrazolidinone or pyrrolidinone. Further, the ring Am can be fused with 5 to 7 membered saturated or unsaturated ring to form, for example, 2-oxo-1,2,3,5,6,7,8, 8a-octahydroimidazo[1,2-a]pyridine-3-spiro-4'-piperidino.

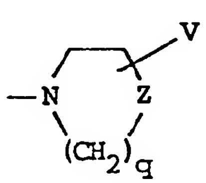
In the above definitions, each (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents (e.g halogen, nitro, amino, cyano, haloalkyl, hydroxyl, alkyl, alkoxy or alkenyl).

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) include salts such as hydrochloride, hydrobromide, phosphate, sulfate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, citrate, lactate, maleate, fumarate, tartrate or oxalate. The present invention also includes hydrate and solvate of the compounds of formula (I).

The compounds of formula (I) or (II-a) to (II-e) having a chiral carbon atom can be prepared as a racemate or an optically active isomer, and the compound having at least two chiral atoms can be obtained as an individual diastereomer or a mixture thereof. The present invention includes the mixture thereof and the individual isomers. Furthermore, the present invention also includes stereomers.

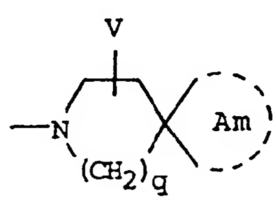
Preferred compounds of the present invention are those of formula (I) wherein T is -NHRa where Ra is heteroarylalkyl which may be optionally substituted by 1 to 3 substituents, or -N(Rb)(Rc) where Rb and Rc are the same or different and each is alkyl, arylalkyl or heteroarylalkyl, or Rb and Rc together with the adjacent nitrogen atom form a cyclic amino of the formula:

(1)



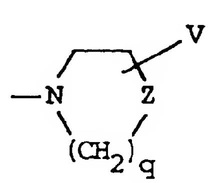
or

(2)

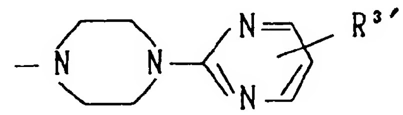


wherein q is an integer of 1 to 4, Z is methylene or N-R^5 (R^5 is aryl, diarylalkyl, heteroaryl, heteroarylalkyl or acyl), substituent V is hydrogen, hydroxyl, carbamoyl, cyclic amino, aryl, arylalkylamino, heteroaryl or bisarylmethylene and the number of V is 1 to 4. cyclic amino of formula (1) may contain carbonyl group in the cycle and further may be fused with aryl or heteroaryl, ring Am of formula (2) contains amido bond in the cycle and further may contain sulfur atom and/or N-R^6 (R^6 is phenyl). Further, the ring Am can be fused with a 5 to 7 membered saturated or unsaturated ring. In the above definitions, (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents.

A preferred definition of T is a cyclic amino of the formula:



where Z is N-R^5 (R^5 is pyrimidinyl or substituted pyrimidinyl), substituent V is hydrogen, and q is 2, that is, the formula (1) is represented by the formula:



wherein R^3 is hydrogen, halogen, nitro, amino, cyano, hydroxyl, alkyl, alkoxy or haloalkyl.

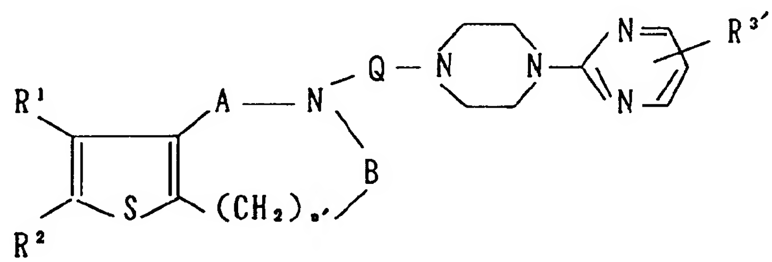
Preferred definitions of E^1, E^2 and E^3 are that E^1 is C-R^1, E^2 is C-R^2 and E^3 is sulfur atom, wherein R^1 and R^2 are as defined above, preferably they are the same or different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, arylalkyl, acyl, alkoxyalkyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, hydroxyalkanoyl, aryloxyalkanoyl or haloalkanoy.

Preferred definitions of A, B and n are that A and B are carbonyl and n is 1 or 2, or one of A and B is absent and the other is carbonyl and n is 2 or 3, and more preferably one of A and B is absent and the other is carbonyl and n is 2.

A preferred definition of Q is straight or branched chain alkylene having 1 to 10 carbon atoms, and more preferably Q is alkylene having 1 to 8 carbon atoms.

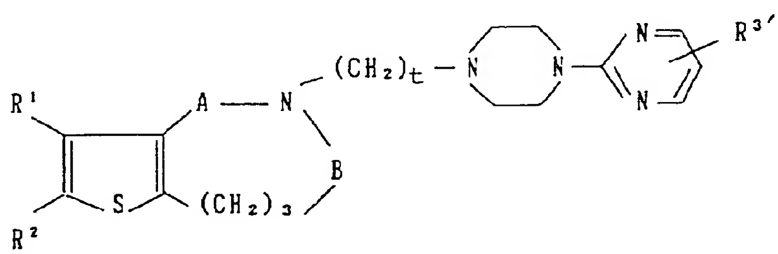
A more preferred definition of D is -CH_2-.

This invention also provides a compound of the formula:



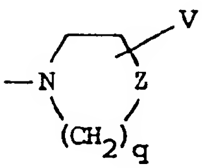
or pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 are the same or different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, aralkyl, acyl, alkoxyalkyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, hydroxyalkanoyl, aryloxyalkanoyl or haloalkanoyl, $R^{3}{}'$ is as defined in claim 6, A and B are carbonyl groups, or one of A and B is absent and the other is carbonyl group, n' is 2 or 3 when A and B are carbonyl groups and n' is 3 or 4 in the other case, Q is straight or branched chain alkylene having 1 to 10 carbon atoms.

This invention further provides a compound of the formula:



or pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 are as defined above, $R^{3}{}'$ is as defined above, t is an integer of 1 to 8, A and B are absent or carbonyl groups with the provisos that when A is absent, B is carbonyl group, and when A is carbonyl group, B is absent.

This invention furthermore provides a compound of the formula (I) or pharmaceutically acceptable acid addition salt thereof, wherein T is a group of the formula:

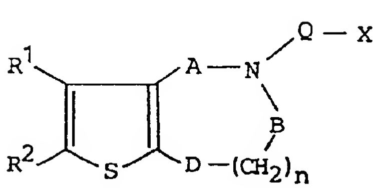


wherein Z is methylene or N-R^5 (R^5 is aryl, diarylalkyl, heteroaryl except pyrimidinyl, heroarylalkyl or acyl), substituent V is hydrogen, hydroxyl, carbamoyl, cyclic amino, aryl, arylalkylamino, heteroaryl or bisarylmethylene and the number of V is 1 to 4, q is 2, and in the above definition the (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents.

Preferred compounds of the formula (I) are 2-bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c] azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c] azepin-4-one,
2-ethyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c] azepin-4-one,
2 acetyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c] azepin-4-one,
2-(1-hydroxyethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c] azepin-4-one,
5-[4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl]-2-methy-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-[4-[(1,4-benzodioxan-2-yl)methylamino]butyl]-2-methy-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-bromo-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-ethyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
4-[4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl]-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one,
5-[4-(4-(bis(4-fluorophenyl)methyl)-1-piperazinyl)butyl]-2-methy-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepine-4,6-dione,
7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihycro-4H-thieno[3,2-f][1,4]thiazepine-3,5-dione,
5-[4-(4-(3-trifluoromethylphenyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-[4-(4-(2,3-dimethylphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-[4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-methoxyphenyl)-1-piperadinyl)butyl]-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one and
4-[4-(4-(bis(4-fluorophenyl)methylene)piperidino)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one or pharmaceutically acceptable acid addition salt thereof.

More preferred compounds of the formula (I) are 2-bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-]azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-ethyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-acetyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-(1-hydroxyethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-bromo-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-ethyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepine-4,6-dione and
7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydro-4H-thieno[3,2-f][1,4]thiazepine-3,5-dione or pharmaceutically acceptable acid addition salt thereof.

Preferred intermediates of the present invention are those of formulas (II) and (IV) wherein E^1 is C-R^1, E^2 is C-R^2 and E^3 is sulfur atom, that is, represented by the formulas:



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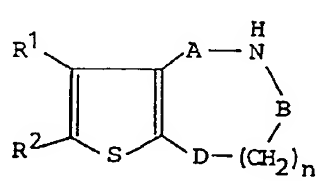


wherein each symbol is as defined above.

The present invention provides a pharmaceutical composition comprising a fused thiophene compound of the formula (I) or pharmaceutically acceptable acid addition salt thereof and a pharmaceutical carrier etc., especially an antianxiety drug, an antipsychotic drug or a drug for a disease of circulatory system.

The methods for preparing the compounds of present invention are described as follows:

Method (1)

The compounds of formula (I) can be synthesized by reacting the compound of formula (II-a) with a compound of formula:

H-T (III)

wherein T is as defined above, or acid addition salt thereof.

The reaction is carried out in an inert solvent such as methanol, ethanol, propanol, benzene, toluene, dimethylformamide, tetrahydrofuran, acetonitrile or acetone in the presence of a suitable acid scavenger (e.g. potassium carbonate, sodium carbonate, sodium hydrogencarbonate, pyridine, triethylamine, sodium acetate or potassium acetate) at 20°C-150°C for 30 minutes to 30 hours.

When X in the compounds of formula (II-a) is hydroxyl, the reaction is carried out in a suitable inert solvent such as dimethylformamide or benzene in the presence of an aminophosphonium reagent (N,N-methylphenylaminotriphenylphosphonium iodide) at 20°C-150°C for 30 minutes to 5 hours.

Method (2)

The compounds of formula (I) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

X-Q-T (V)

wherein each symbol is as defined above, or an acid addition salt thereof.

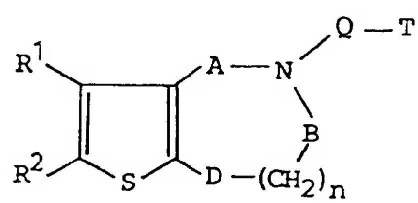
The reaction is carried out under the same condition as the method (1).

Method (3)

The compounds of formula (I) can be prepared by reductive amination of the compound of formula (II-b) with a compound of formula (III).

The reaction is carried out in an alcohol solvent such as methanol, ethanol or propanol in the presence of a suitable reductant (e.g. sodium borohydride, sodium cyanoborohydride) at 0°C to the boiling point of the solvent employed for 1 to 24 hours.

In the compounds of formula (I), for example, the compounds of formula:

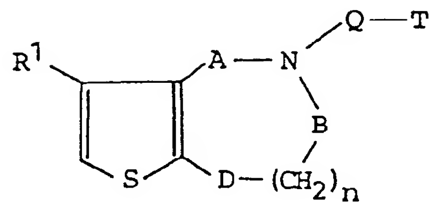


(I')

wherein R^2 is acyl or a group derived from acyl and other symbols are as defined above, can be synthesized by the following methods.

Method (4)

The compounds of formula (I') wherein R^2 is acyl can be synthesized by reacting a compound of the formula:



(VI)

wherein each symbol is as defined above, with a compound of the formula:

R^4COOH (VII)

wherein R^4 is alkyl, aryl, haloalkyl, pyridyl, thienyl or furyl.

The reaction is carried out in a suitable inert solvent such as benzene or toluene or without solvent in the presence of a dehydrating agent (e.g. polyphosphoric acid, phosphorus pentoxide) at 10°C-150°C.

Method (5)

The compound of formula (I') wherein R^2 is acyl can be synthesized by reacting the compound of formula (VI) with a compound of the formula:

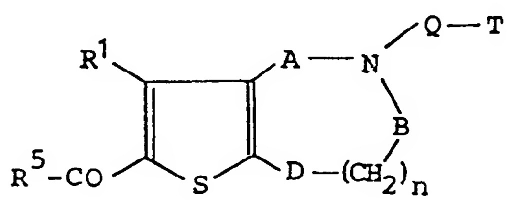
R^4COZ (VIII)

wherein Z is halogen and R^4 is as defined above.

The reaction is carried out in a suitable inert solvent such as benzene, toluene, chloroform, dichloromethane or dichloroethane in the presence of a suitable Lewis acid (e.g. tin chloride, iron chloride, aluminum chloride, zinc chloride) at -10°C to 100°C for 30 minutes to 5 hours.

Method (6)

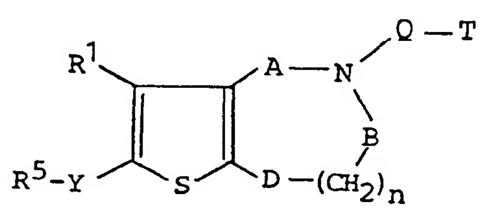
The compounds of formula (I') wherein R^2 is alkyl, aralkyl or 1-hydroxyalkyl can be synthesized by reducing a compound of the formula:



(IX)

wherein R^5 is alkyl, aralkyl or aryl and other symbols are as defined above, with a reductant such as sodium borohydride, lithium aluminum hydride or triethylsilane, or by subjecting the compound to catalytic reduction in the presence of a suitable catalyst (e.g. platinum dioxide, palladium, rhodium).

The reaction is carried out in a suitable solvent (e.g. methanol, ethanol, propanol, butanol, acetic acid) at -10°C to 150°C to give a compound of the formula:

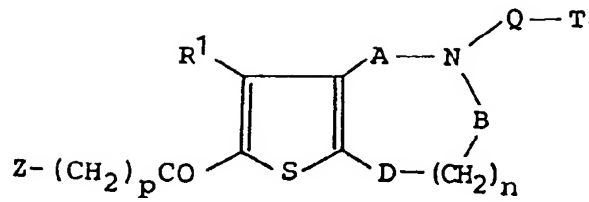


(X)

wherein Y is -CH(OH)- or $-CH_2-$ and other symbols are as defined above.

Method (7)

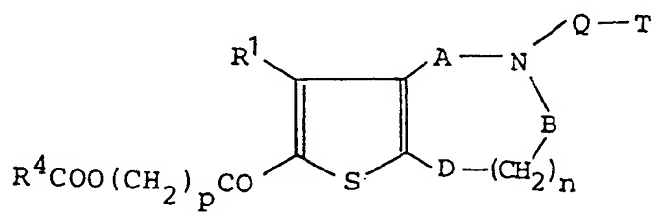
The compounds of formula (I') wherein R^2 is acyloxyalkanoyl can be synthesized by reacting a compound of the formula:



(XI)

wherein p is a integer of 1 to 4 and other symbols are as defined above, with a metal (e.g. sodium, potassium, lithium) salt of a compound of the formula (VII).

The reaction is carried out in a suitable inert solvent such as chloroform, methylene chloride, benzene, toluene or dimethylformamide at room temperature to 150°C for 1 to 20 hours to give a compound of the formula:



(XII)

wherein each symbol is as defined above.

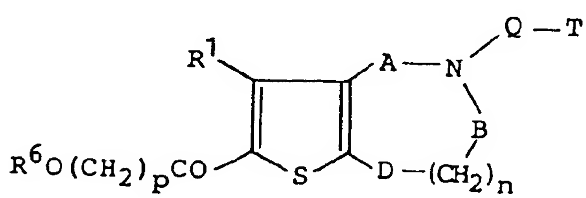
Method (8)

The compounds of formula (I') wherein R^2 is alkoxyalkanoyl or aryloxyalkanoyl can be synthesized by reacting the compound of formula (XI) with a metal (e.g. sodium, potassium, lithium) salt of a compound of the formula:

R^6OH (XIII)

wherein R^6 is alkyl or aryl.

The reaction is carried out in a suitable inert solvent such as tetrahydrofuran, benzene, toluene or dimethylformamide at room temperature to 150°C for 1 to 20 hours to give a compound of the formula:



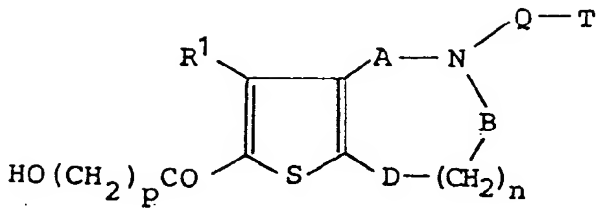
(XIV)

wherein each symbol is as defined above.

Method (9)

The compounds of formula (I') wherein R^2 is hydroxyalkanoyloxy can be synthesized by hydrolysis of the compound of formula (XII).

The reaction is carried out in a suitable inert solvent such as methanol, ethanol, propanol, butanol or water in the presence of an aqueous solution of an acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid) or an alkali (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, potassium carbonate) at -10°C to 150°C for 1 to 20 hours to give a compound of the formula:

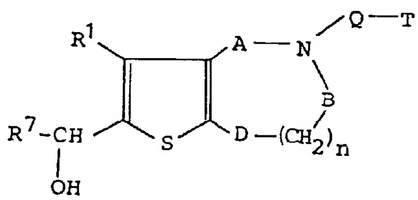


(XV)

wherein each symbol is as defined above.

Method (10)

The compounds of formula (I') wherein R^2 is acyloxyalkyl or alkoxyalkyl can be synthesized by reacting a compound of the formula:



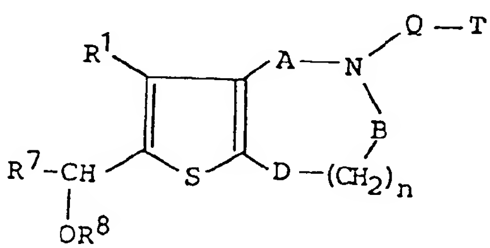
(XVI)

wherein R^7 is alkyl and other are as defined above, which is obtained in method (6) with a compound of the formula:

$$R^8Z \quad (XVII)$$

wherein R^8 is acyl or alkyl and Z is as defined above.

The reaction is carried out in a suitable inert solvent such as methanol, ethanol, propanol, butanol, dimethylformamide, tetrahydrofuran, benzene or toluene in the presence of an acid scavenger (e.g. sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium hydroxide, sodium hydroxide) at room temperature to 150°C for 1 to 20 hours to give a compound of the formula:



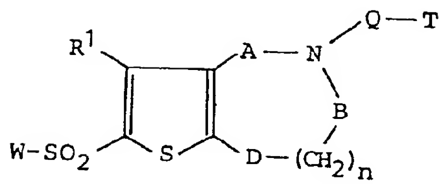
(XVIII)

wherein each symbol is as defined above.

Method (11)

The compounds of formula (I') wherein R^2 is hydroxysulfonyl or halosulfonyl can be synthesized by reacting the compound of formula (VI) with sulfuric acid or halosulfonic acid.

The reaction is carried out in a suitable inert solvent such as benzene or toluene or without solvent at -10°C to 100°C to give the compound of formula:



(XIX)

wherein W is hydroxyl or halogen and other symbols are as defined above.

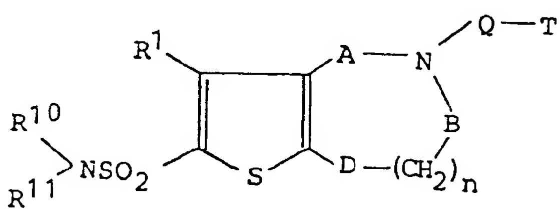
Method (12)

The compounds of formula (I′) wherein R^2 is sulfamoyl or substituted-sulfamoyl can be synthesized by reacting the compound of formula (XIX) with the compound of formula:

$$HN(R^{10})(R^{11}) \quad (XX)$$

wherein R^{10} and R^{11} are the same or different and each is hydrogen, alkyl, arylalkyl or aryl.

The reaction is carried out in a suitable inert solvent such as benzene, toluene, dimethylformamide or tetrahydrofuran, preferably in the presence of an acid scavenger (e.g. sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium hydroxide, sodium hydroxide) at -10°C to 150°C for 1 to 20 hours to give the compound of formula:



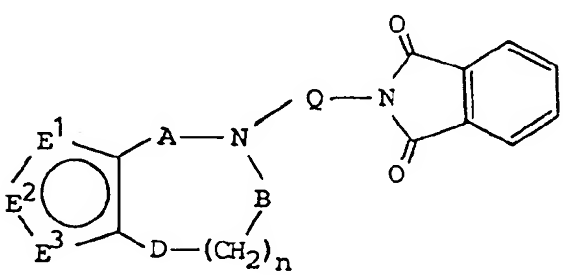
(XXI)

wherein each symbol is as defined above.

The above-mentioned methods of (4) to (12) are also applicable to the syntheses of compounds of formula (I) (wherein E^1=C-R^1, E^2=sulfur atom, E^3=C-R^2; or E^1=sulfur atom, E^2=C-R^1, E^3=C-R^2) other than formula (I′).

Method (13)

The compounds of formula (I) wherein T is amino group ($-NH_2$) can be synthesized by reacting a compound of the formula:



(I-a)

wherein each symbol is as defined above, which can be obtained by the above method, in an inert solvent (e.g. methanol) in the presence of hydrazine hydrate at 20°C to 150°C for 1 to 20 hours.

Method (14)

The compounds of formula (I) wherein T is amino group ($-NH_2$) can be synthesized by reacting the compound of formula (II-c) or (II-e) in an inert solvent (e.g. lower alcohol such as methanol, ethanol or propanol,

water, acetic acid, tetrahydrofuran, dioxane) in the presence of a nickel catalyst such as Raney nickel at 0°C to the boiling point of the solvent employed for 1 to 24 hours.

Method (15)

The compounds of formula (I) wherein T is amino group ($-NH_2$) can be synthesized by reacting the compound of formula (II-d) in an inert solvent (e.g. water) in the presence of bromine and sodium hydroxide or potassium hydroxide at 0°C to 100°C for 1 to 24 hours.

The compounds of formula (II-a) which are synthetic intermediates are novel compounds and can be prepared by the following method.

Method (16)

The compounds of formula (II-a) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

$$X^1\text{-}Q\text{-}X^2 \quad \text{(XXII)}$$

wherein X^1 and X^2 are hydroxyl or reactive atom or group derived from hydroxyl (e.g. halogen, methanesulfonyloxy, paratoluenesulfonyloxy) with the proviso that both X^1 and X^2 are not hydroxyl at the same time and Q is as defined above.

The reaction is carried out in a suitable inert solvent such as methanol, ethanol, propanol, dimethylformamide, benzene, toluene, tetrahydrofuran or acetonitrile in the presence of a suitable base (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate) at -20°C to 150°C for 30 minutes to 5 hours.

The compounds of formula (II-b) which are synthetic intermediates are also novel compounds and can be prepared by the following method.

Method (17)

The compounds of formula (II-b) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

$$X^3\text{-}Q\text{-}COR^4 \quad \text{(XXIII)}$$

wherein X^3 is a removable group such as chlorine, bromine, iodine, methanesulfonyloxy or paratoluenesulfonyloxy and other symbols are as defined above, or preferably by protecting the carbonyl group of the compound (XXIII) in a conventional manner of organic chemistry, reacting with the compound of formula (IV) and then eliminating the protecting group to give the objective compound in good yield.

The reaction is carried out in a suitable inert solvent such as dimethylformamide, methanol, ethanol, propanol, butanol, tetrahydrofuran, benzene, toluene or acetonitrile in the presence of a suitable base (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate) at -20°C to 150°C for 30 minutes to 5 hours.

The synthetic intermediate compounds of formula (II-a) wherein R^2 is acyl, alkyl, aralkyl, 1-hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, aryloxyalkanoyl, hydroxyalkanoyl, acyloxyalkanoyl, alkoxyalkyl, hydroxysulfonyl, halosulfonyl, aminosulfonyl or substituted-aminosulfonyl can be prepared by applying the above-mentioned methods (4) to (12) to the compound of formula (II-a). The methods (4) to (12) can also be applied to the synthetic intermediate compounds of formula (II-b).

The compounds of formulas (II-c), (II-d) and (II-e) which are synthetic intermediates are novel compounds and can be prepared by the following methods.

Method (18)

The compounds of formula (II-c) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

$$X^3\text{-}Q\text{-}CN \quad \text{(XXIV)}$$

wherein each symbol is as defined above.

The reaction is carried out in a suitable inert solvent such as dimethylformamide, methanol, ethanol, propanol, tetrahydrofuran, benzene, toluene or acetonitrile in the presence of a suitable base (e.g. sodium methoxide, sodium ethoxide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate) at -20°C to 150°C for 30 minutes to 5 hours.

Method (19)

The compounds of formula (II-d) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

$$X^3\text{-Q-CONH}_2 \quad \text{(XXV)}$$

wherein each symbol is as defined above.

The reaction is carried out under the same condition as in the method (18).

Method (20)

The compounds of formula (II-e) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:

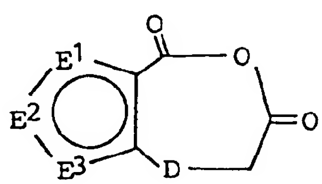
$$X^3\text{-Q-NO}_2 \quad \text{(XXVI)}$$

wherein each symbol is as defined above.

The reaction is carried out under the same condition as in the method (18).

Method (21)

The compounds of formula (I) wherein both A and B are carbonyl groups can, for example, be synthesized by subjecting a compound of the formula:



(XXVII)

wherein each symbol is as defined above, with a compound of the formula:

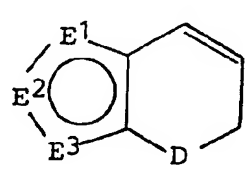
$$H_2N\text{-Q-T} \quad \text{(XXVIII)}$$

wherein each symbol is as defined above, to dehydrating reaction.

The reaction is carried out in a suitable inert solvent (e.g. acetic anhydride, toluene, benzene, chloroform, methylene chloride, pyridine, methanol, ethanol, isopropyl alcohol, dimethylformamide, tetrahydrofuran) or without a solvent at 20°C to the boiling point of the solvent employed for 30 minutes to 10 hours.

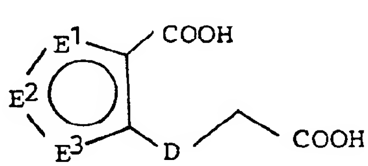
Method (22)

The compounds of formula (XXVII) are novel and can be synthesized by reacting, for example, a compound of the formula:



(XXIX)

wherein each symbol is as defined above, with ozone and then subjecting a resulting compound of the formula:



(XXX)

wherein each symbol is as defined above, obtained by the oxidative treatment to ring closure reaction with a

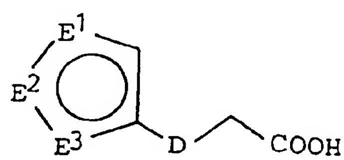
dehydrating agent (e.g. phosphorus pentoxide, dicyclohexylcarbodiimide, N,N-carbonyldiimidazole, acid anhydride, acid halide, benzenesulfonyl chloride).

The reaction of the compound of formula (XXIX) with ozone is carried out in a suitable inert solvent such as methanol, ethanol, propanol or tetrahydrofuran at -20°C to 150°C for 30 minutes to 10 hours.

The reaction of the compound of formula (XXX) with a dehydrating agent is carried out in a suitable inert solvent (e.g. ether, dichloromethane, tetrahydrofuran) or without a solvent at 10°C to 150°C for 30 minutes to 10 hours.

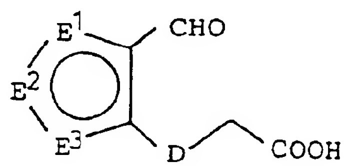
Method (23)

The compounds of formula (XXVII) can also be synthesized by introducing formyl group into, for example, a compound of the formula:



(XXXI)

wherein each symbol is as defined above, by Vilsmeier reaction or the like and oxidating the formyl group of a compound of the formula:



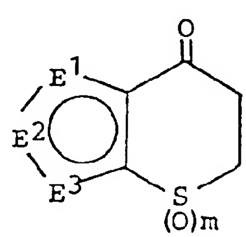
(XXXII)

wherein each symbol is as defined above, by a conventional method employed in organic chemistry and then treating the resulting compound of formula (XXX) in the same manner as the above method (23).

The compounds of formula (IV) wherein D is $S(O)_m$ and A is absent, B is carbonyl or A is carbonyl , B is absent are also novel and can be synthesized by, for example, the following method (24) or (25).

Method (24)

A method which comprises subjecting a compound of the formula:



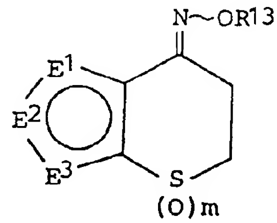
(XXXIII)

wherein each symbol is as defined above, to Schmidt rearrangement.

The reaction is carried out by reacting with sodium azide in a suitable inert solvent such as chloroform, methylene chloride, toluene or benzene or without a solvent in the presence of a suitable acid (e.g trifluoroacetic acid, polyphosphoric acid, sulfuric acid) at 0°C to 150°C for 30 minutes to 10 hours.

Method (25)

A method which comprises subjecting a compound of the formula:



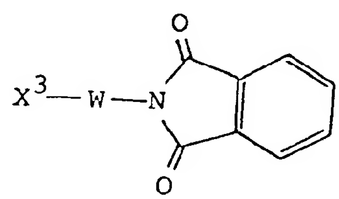
(XXXIV)

wherein R^{13} is hydrogen, alkyl, methanesulfonyl group or paratoluenesulfonyl group and other symbols are as defined above, to Beckmann rearrangement.

The reaction is carried out in a suitable inert solvent such as benzene, toluene, dimethylformamide or diethyl ether or without a solvent in the presence of a suitable acid (e.g. polyphosphoric acid, sulfuric acid, phosphoric acid, phosphorus oxychloride, phosphorus pentachloride, phosphorus pentoxide) at 0°C to 150°C for 30 minutes to 10 hours.

Method (26)

The compounds of formula (I-a) which are used in method (13) can be synthesized by reacting the compound of formula (IV) with a compound of the formula:



(XXXV)

wherein each symbol is as defined above.

The reaction is carried out under the same condition as method (18).

Method (27)

The compounds of formula (I) wherein A and/or B are(is) thiocarbonyl group can be synthesized by reacting the compound of formula (I) wherein A and/or B are(is) carbonyl group with a thionating agent. The thionating agent includes phosphorus pentasulfide, Lawesson reagent [2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetan-2,4-disulfide] and so on. The reaction is usually carried out in an inert solvent (e.g. pyridine, dimethylaniline, benzene, toluene, xylene, tetrahydrofuran, chloroform, dioxane or a mixed solvent thereof) at 30°C to 100°C.

Method (28)

The compounds of formula (I) wherein R^1 and/or R^2 are(is) acylamino can be synthesized by a well known acylation of the compounds wherein R^1 and/or R^2 are(is) amino, or by first reacting the compounds of formula (I) wherein R^1 and/or R^2 are(is) acyl with a hydroxylamine and then subjecting the obtained oxime compounds to a Beckmann rearrangement, or by subjecting the compounds of formula (I) wherein R^1 and/or R^2 are(is) acyl to a Schmidt rearrangement.

The method for synthesizing the oxime compounds is carried out by reacting the compounds of formula (I) wherein R^1 and/or R^2 are(is) acyl with a hydroxylamine hydrochloride in a suitable inert solvent (e.g. benzene, toluene, chloroform, methylene chloride, dimethylformamide, tetrahydrofuran, methanol, ethanol) in the presence of a base (e.g. potassium carbonate, sodium hydrogencarbonate, sodium hydroxide, potassium hydroxide, triethylamine) at room temperature to refluxing temperature of the solvent employed.

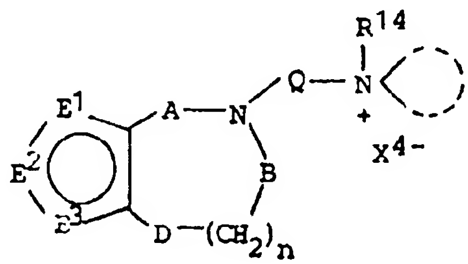
The Beckmann rearrangement is carried out by reacting the above oxime compounds in a polyphosphoric acid at 60°C to 120°C.

The Schmidt rearrangment is carried out by reacting the compounds of formula (I) wherein R^1 and/or R^2

are(is) acyl with sodium azide in polyphosphoric acid or sulfuric acid at 0°C to 100°C.

Method (29)

The compounds of formula (I) can be synthetized by reacting a compound of the formula:



(XXXVI)

wherein R^{14} is alkyl and X^4 is halogen, and other symbols are as defined above, with the compound of formula (III).

The reaction is carried out in a suitable inert solvent such as methanol, etharol, benzene, toluene, dimethylformamide or 1,3-dimethyl-2-imidazolidinone at 50°C to 150°C for 1 to 10 hours.

Method (30)

The compounds of formula (XXXVI) can be synthesized by reacting the compound of formula (I) wherein T is tertiary amino group with a compound of the formula:

$R^{14}X^4$ (XXXVII)

wherein each symbol is as defined above.

The reaction is carried out in a suitable inert solvent (e.g. benzene, toluene, acetone, chloroform, methylene chloride, dimethylformamide, tetrahydrofuran, methanol, ethanol, acetonitrile) at -20°C to refluxing temperature of the solvent employed for 10 minutes to 5 hours.

Method (31)

The compound of formula (I) wherein T is $-NH_2$ is reacted with a compound of the formula:

$R^{16}X^3$ (XXXVIII)

wherein R^{15} is alky or arylalkyl and X^3 is as defined above, to give a compound of the formula (I) wherein T is $-NHR^{15}$ or $-N(R^{15})$ (R^{15}) (R^{15} is as defined above).

The reaction is carried out in a suitable inert solvent (e.g. methanol, ethanol, propanol, dimethylformamide, tetrahydrofuran, benzene or toluene) in the presence of a suitable acid scavenger (e.g. triethylamine, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide) at 0°C to the boiling point of the solvent employed.

Further, the compound of formula (I) wherein T is $-NHR^{15}$ is reacted with a compound of the formula :

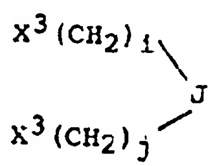
$R^{16}X^3$ (XXXIX)

wherein R^{16} is alkyl or arylalkyl and X^3 is a defined above, to give a compound of the formula (I) wherein T is $-N(R^{16})$ (R^{16}) (R^{15} and R^{16} are as defined above).

The reaction is carried out under the same condition as the above.

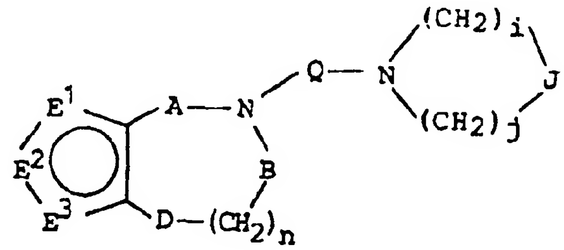
Method (32)

The compound of formula (I) wherein T is $-NH_2$ is reacted with a compound of the formula:



(XXXX)

wherein i and j are integer of 1 to 3 respectively, J is oxigen atom, sulfur atom, CH-R^{17} or N-R^{17} (R^{17} is hydrogen, alkyl, arylalkyl or heteroaryl) and X^3 ia as defined above, to give a compound of the formula (I) represented by:



wherein each symbol is as defined above.

The reaction is carried out in a suitable inert solvent (e.g. methanol, ethanol, propanol, dimethylformamide, tetrahydrofuran, benzene or toluene) in the presence of a suitable acid scavenger (e.g. triethylamide, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide) at 0°C to the boiling point of the solvent employed.

The thus obtained compounds of present invention can be isolated and purified by a conventional method such as recrystallization or column chromatography.

When the obtained compound is a racemate, it can be separated into desired optically active isomers, for example, by means of fractional recrystallization of a salt with an optically active acid or through column filled with an optically active carrier. Individual diastereomers can be separated by the method such as fractional crystallization or chromatography. Such compounds can also be obtained by using an optically active starting material. Furthermore, the stereoisomers can be isolated by recrystallization, column chromatography or the like.

The following experiments will illustrate potent pharmacological activities of the compounds of formula (I).

Experiment 1: Affinity for serotonin 1A (5-HT_{1A}) receptor [^{3}H-8-Hydroxy-2-dipropylaminotetralin (^{3}H-8-OH-DPAT) binding test]

Preparation of crude synaptosome fraction and binding assay were conducted in accordance with the method reported in Journal of Neurochemistry, vol. 44, page 1685, 1985 by Hall et al. Freezed hippocampus dissected out from rats were homogenized in 40 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) and the suspension was centrifuged at 500 x g for 10 minutes at 0°C. The supernatant was centrifuged at 40,000 x g for 20 minutes at 0°C and the resulting pellet was homogenized in 40 volumes of the above buffer and incubated at 37°C for 10 minutes. After completion of reaction, the suspension was centrifuged at 40,000 x g for 20 minutes at 0°C. The resulting pellet was washed twice by resuspension in 40 volumes of the above buffer and centrifugation, and finally suspended in 60 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) containing 1 mM manganese chloride for use in the next assay.

To the aliquots (900 μ l) of synaptosome membranes solution were added 50 μ l of tririated 8-OH-DPAT solution at the terminal concentration of 0.2 nM and 50μ l of test compound solution or 50μ l of its medium, and incubated at 37°C for 10 minutes. Then, to the mixture was added 5 ml of ice-cold 50 mM Tris-HCl buffer (pH 7.4), rapidly vacuum-filtered through Whatman GF/B filters and washed twice with 5 ml of the same buffer. The radioactivity of the residue remaining on the filters was measured by liquid scintillation counter. Nonspecific binding was determined under the presence of 10^{-5} M serotonin (5-HT). 50% Inhibition concentration (IC_{50}) of the test compound was graphically determined and the inhibition constant (Ki value) was calculated. The results are summarized in Table A.

Experiment 2: Affinity for serotonin 2 (5-HT_2) receptor (^{3}H-Ketanserin binding test)

Preparation of crude synaptosome fraction and binding assay were conducted according to the method reported in Molecular Pharmacology, vol. 21, page 301, 1981 by Leysen et al.

Freezed cerebral cortex dissected out from rats were homogenized in 30 volumes of ice-cold 0.32 M sucrose solution and the suspension was centrifuged at 1000 x g for 10 minutes at 0°C. The supernatant was centrifuged at 40,000 x g for 20 minutes at 0°C and the resulting pellet was homogenized in 30 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.7), and incubated at 37°C for 10 minutes. The suspension was centrifuged at 40,000 x g for 20 minutes at 0°C again. The resulting pellet was homogenized in 100 volumes of the above

buffer and provided as synaptosome membranes solution for the next assay.

To the aliquots (900μ l) of synaptosome membranes solution were added 50μ l of ^{3}H-Ketanserin solution at the terminal concentration of 0.2 nM and 50μ l of test compound solution or 50μ l of its medium, and incubated at 37°C for 20 minutes. After completion of the reaction, the mixture was rapidly vacuum-filtered through Whatman GF/B filters. The filters were washed three times with 5 ml of the above buffer, and then the radioactivity of the residue remaining on the filters was measured by liquid scintillation counter. Nonspecific binding was determined under the presence of 10μ M of mianserin. 50% Inhibition concentration (IC_{50}) of the test compound was graphically determined and the inhibition constant (Ki value) was calculated. The results are summarized in Table A.

Experiment 3: Affinity for dopamine 2 (D_2) receptor (^{3}H-Spiperone binding test)

Preparation of crude synaptosome fraction and binding assay were conducted in accordance with the method reported in European Journal of Pharmacology, vol. 46, page 377, 1977 by I. Creese et al. Freezed corpus striatum dissected out from rats were homogenized in 100 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.7) and the suspension was centrifuged at 500 x g for 10 minutes at 0°C. The supernatant was centrifuged at 50,000 x g for 15 minutes at 0°C and the resulting pellet was homogenized in 100 volumes of the above buffer, and then the suspension was centrifuged at 50,000 x g for 15 minutes at 0°C again. The resulting pellet was homogenized in 150 volumes of 50 mM Tris-HCl buffer (pH 7.1) containing 120 mM sodium chloride, 5 mM potassium chloride, 2 mM calcium chloride, 1 mM magnesium chloride, 0.1% ascorbic acid and 10μ M pargyline. The suspension was incubated at 37°C for 10 minutes and then provided as synaptosome membranes solution for the next assay.

To the aliquots (900 μ l) of synaptosome membranes solution were added 50μ l of ^{3}H-Spiperone solution at the terminal concentration of 0.2 nM and 50μ l of test compound solution or 50μ l of its medium, and incubated at 37°C for 20 minutes. After completion of the reaction, the mixture was rapidly vacuum-filtered through Whatman GF/B filters. The filters were washed three times with 5 ml of the above buffer, and then the radioactivity of the residue remaining on the filters was measured by liquid scintillation counter. Nonspecific binding was determined under the presence of 100μ M of (±)-Sulpiride. 50% Inhibition concentration (IC_{50}) of the test compound was graphically determined and the inhibition constant (Ki value) was calculated. The results are summarized in Table A.

Table A

Example No. of test compound	Receptor binding Ki (nM)		
	5-HT_{1A}	5-HT_2	D_2
11	0.89	900.0	100.0
13 (maleate)	1.6	1400.0	190.0
15 (hydrochloride)	2.1	1500.0	140.0
46	1.3	990.0	78.0
103	5.2	1800.0	1800.0
107	1.5	990.0	120.0
117	4.1	1800.0	270.0
121	1.4	1100.0	150.0
155	0.81	2100.0	170.0
163	0.15	1200.0	6.2

Experiment 4: Anxiolytic effect (Vogel type conflict test)

The test was conducted according to the method of Vogel et al. Wistar rats deprived of water for 72 hours before the test were used. The rats were placed in a plexiglas conflict test box (light compartment : 38 x 38 x 20 cm, dark compartment: 10 x 10 x 20 cm). A water bottle with a stainless steel spout was fitted to the middle of the outside, so that the spout extended 3 cm into the box at a height of 10 cm above the grid floor. A drinkometer circuit (Ohara Inc., Nihon Koden) was connected with the spout and the number of licks were counted. The rat was placed into the apparatus where an electric shock (0.2-0.3 mA, 0.3 sec) was given once every 20th lick. After the rat received first electric shock, the number of shocks were recorded during the subsequent 3 min. test period. The test compounds were administered orally 1 hour before the test. The minimum effective dose (MED) was defined as the lowest dose producing a statistically significant difference between 0.5% MC-treated (control) and test drug treated punished responses (One-way ANOVA test; $P< 0.05$). The results are summarized in Table B.

Table B

Example No. of test compound	Anxiolytic effect MED (mg/kg, p.o.)
13 (maleate)	1.0
15 (hydrochloride)	2.5
46	≦ 1.0
117	5.0
155	2.5
163	2.5

Experiment 5: Toxicity

All ddY male mice survived after five days following the oral (1000 mg/kg) and the intraperitoneal (300 mg/kg) administration of the test compounds of the present invention.

From the results of various pharmacological experiments, the compounds (I) of the present invention have high affinity for serotonin 1.A (5-HT_{1A}), serotonin 2 (5-HT_2) and/or dopamine 2 (D_2) receptors. Among them, compounds having selective high affinity for 5-HT_{1A} receptor are useful as potent antianxietic drug with less side effects in the extrapyramidal system (EPS). The compounds having high affinity for not only D_2 receptor but also 5-HT_{1A} and 5-HT_2 receptors are useful as antipsychotic drug which are effective on negative symptoms such as apathy, abulia or disorder of cognition as well as on positive symptoms such as hallucination, delusion or psychomotor excitement with reduced side effects, for example, EPS. Further, the compounds of the present invention can also be used as drugs for the disease of circulatory system, such as antihypertensive drug which lower arterial pressure and decrease heart rate by interacting with 5-HT_{1A} receptors.

When the compounds of formula (I) of the present invention are used as pharmaceuticals, a therapeutically effective amount of the compounds and adequate pharmacologically acceptable additives such as excipient, carrier, diluent and so on are mixed to be formulated into a form such as tablets, capsules, granules, syrups, injectable solutions, suppositories, dispersible powders or the like and are administered in the form mentioned above. The dosage may generally range about 5 to about 500 mg per day for an adult in a single dose or divided doses in the case of oral administration.

Formulation Example of the Pharmaceutical Composition:

Tablets containing 10 mg of the compound of formula (I) can be prepared by the following composition.

Compound (I)	10.0 mg
Lactose	58.5 mg
Corn starch	25.0 mg
Crystalline cellulose	20.0 mg
Polyvinyl pyrrolidone K-30	2.0 mg
Talc	4.0 mg
Magnesium stearate	0.5 mg
	120.0 mg

Compound (I) is pulverized with an atomizer to make fine powder having an average particle size below 10μ. The fine powder of compound (I), lactose, corn starch and crystalline cellulose are mixed well in a kneader and then kneaded with a binder paste prepared by polyvinyl pyrrolidone K-30. The wet mass is passed through a 200 mesh sieve and then dried in an oven at 50°C. The dry granule containing 3 to 4% of water content is forced through a 24 mesh sieve. Talc and magnesium stearate are mixed and compressed into tablets by using a rotatory tableting machine with a flat punch of 8 mm diameter.

The present invention will be explained in more detail by the following examples, but these examples are not to be construed as limiting the present invention.

Example 1

To a solution of 10 g of 5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 120 ml of dimethylformamide was added 8.7 g of potassium t-butoxide with stirring under ice-cooling and the mixture was stirred at room temperature for 2 hours. Then, to the mixture was added 9.0 ml of 4-bromo-1-chlorobutane under ice-cooling and the solution was stirred at room temperature for 4 hours. After completion of the reaction, the reaction mixture was poured into chilled water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel using chloroform as an eluent to give 10.0 g of 5-(4-chlorobuyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]-azepin-4-one as a pale yellow oil.

Example 2

To a solution of 7.4 g of 5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepin -4-one in 70 ml of dimethylformamide is added 6.5 g of potassium t-butoxide with stirring under ice-cooling and the mixture was stirred at room temperature for 2 hours. Then, to the mixture was added 6.6 g of 4-bromo-1-chlorobutane under ice-cooling and the solution was stirred at room temperature for 4 hours. After completion of the reaction, the reaction mixture was poured into chilled water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel using chloroform as an eluent to give 9.5 g of 4-(4-chlorobutyl)-4,6,7,8-tetrahydro-5H-thieno[3,2-b]-azepin-5-one as a pale yellow oil.

The following compounds can be prepared in a similar manner as the above examples:

Example 3

5-(4-Chlorobutyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]-azepin-4-one

Example 4

4-(4-Chlorobutyl)-2-methyl-4,6,7,8-tetrahydro-5H-thieno[3,2-b]-azepin-5-one

Example 5

To a solution of 3.0 g of 5-(4-chlorobutyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 20 ml of acetic acid was added dropwise a solution of 2.1 g of bromine in 5 ml of acetic acid for 10 minutes. After the mixture was stirred at room temperature for 3 hours, the mixture was poured into chilled water and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and then concentrated under reduced pressure to give 4.0 g of 2-bromo-5-(4-chlorobutyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one as a pale brown oil. The obtained compound was employed in the subsequent reaction without purification.

The following compound can be prepared in a similar manner as the above example:

Example 6

2-Bromo-4-(4-chlorobutyl)-4,6,7,8-tetrahydro-5H-thieno[3,2-b]-azepin-5-one

Example 7

To an ice-cooled suspension of 2.8 g of aluminum chloride in 20 ml of dichloromethane was added 1.7 g of acetyl chloride and the mixture was stirred for 10 minutes at the same temperature, and then to the solution was added a solution of 1.8 g of 5-(4-chlorobutyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 5 ml of dichloromethane. The resulting mixture was stirred for 5 hours at room temperature, poured into chilled water and then extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting crystals were recrystallized from the mixed solvent of ethyl acetate and isopropyl ether to give 2-acetyl-5-(4-chlorobutyl)-5,6,7,8-tetrahydro-4H-thino[3, 2-c]azepin-4-one as white crystals, melting at 64-65°C.

The following compound can be prepared in a similar manner as the above example:

Example 8

2-Acetyl-4-(4-chlorobutyl)-4,6,7,8-tetrahydro-5H-thieno[3,2-b]-azepin-5-one

Example 9

To a solution of 3.0 g of 5-(4-chlorobutyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 50 ml of toluene-dimethylformamide (1:1) were added 3.0 g of N-(2-pyrimidinyl)piperazine dihydrochloride, 3.2 g of potassium carbonate and 2.0 g of potassium iodide and the mixture was stirred at 90°C - 100°C for 6 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated in vacuo. The resulting residue was dissolved in ethanol and to the solution was added 1 g of fumaric acid to form fumarate. The crystals were collected by filtration and recrystallized from ethanol to give 3.1 g of 5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate as white crystals, melting at 188-190°C.

The following compounds can be prepared in a similar manner as the above example:

Example 10

4-[4-(4-(2-Pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one fumarate, melting at 164-166°C

Example 11

2-Bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)]butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate, melting at 174-176°C

Example 12

2-Bromo-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one fumarate, melting at 169-172°C

Example 13

2-Acetyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)]butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one, melting at 103-106°C. Its fumarate melts at 166-169°C. Its maleate melts at 161-163°C. Its hydrochloride melts at 205-210°C.

Example 14

2-Acetyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one fumarate, melting at 159-162°C

Example 15

2-Methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)]butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one, melting at 86-88°C. Its fumarate melts at 168-172°C. Its hydrochloride melts at 197-198°C.

Example 16

2-Methyl-5-[6-(4-(2-pyrimidinyl)-1-piperazinyl)]hexyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one maleate, melting at 108-110°C,

Example 17

To a solution of 3.5 g of 2-acetyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one in 35 ml of trifluoroacetic acid was added 2.7 ml of triethylsilane and the mixture was stirred for 20 hours at room temperature. Then, the mixture was poured into water, made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried and concentrated under reduced pressure. The residue was dissolved in acetone and to the solution was added 1.5 g of fumaric acid to produce its fumarate. The precipitated crystals were collected by filtration and recrystallized from ethanol to give 2.0 g of 2-ethyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]-azepin-5-one fumarate as white crystals, melting at 156-158°C.

The compounds shown in the Table 1 and Table 2 can be prepared in a similar manner as the above examples:

Example 42

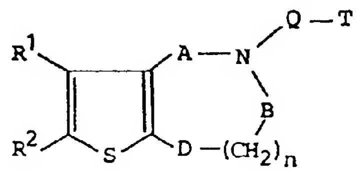
The reaction and procedure were conducted in the same manner as in Example 7 using propionyl chloride in place of acetyl chloride to give 5-(4-chlorobutyl)-5,6,7,8-tetrahydro-2-propionyl-4H-thieno[3,2-c]azepin-4-one as white crystals, melting at 91-92°C.

The following compounds can be prepared in the same manner as in Example 9.

Example 43

2-Methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-

Table 1



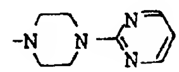
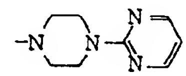
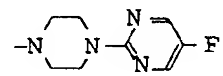
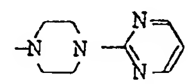
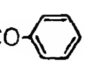
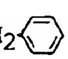
No.	R¹	R²	A	B	D	n	Q	T
18	H	C_2H_5	C=O	–	CH_2	2	$-(CH_2)_4-$	
19	〃	〃	–	C=O	〃	〃	〃	〃
20	〃	C_3H_7	C=O	–	〃	〃	〃	〃
21	〃	〃	–	C=O	〃	〃	〃	〃
22	〃	Cl	C=O	–	〃	〃	〃	〃
23	〃	〃	–	C=O	〃	〃	〃	〃
24	〃	CH_3	C=O	–	〃	〃	$-(CH_2)_2-$	〃
25	〃	〃	–	C=O	〃	〃	〃	〃
26	CH_3	〃	C=O	–	〃	〃	$-(CH_2)_4-$	〃
27	〃	〃	–	C=O	〃	〃	〃	〃
28	H	CHO	C=O	–	〃	〃	〃	〃
29	〃	〃	–	C=O	〃	〃	〃	〃
30	Cl	Cl	C=O	–	〃	〃	〃	〃

Table 2

No.	R^1	R^2	A	B	D	n	Q	T
31	Cl	Cl	–	C=O	CH_2	2	$-(CH_2)_4-$	
32	H	CH_3	C=O	–	〃	〃	〃	
33	〃	〃	–	C=O	〃	〃	〃	〃
34	〃	I	C=O	–	〃	〃	〃	
35	〃	〃	–	C=O	〃	〃	〃	"
36	〃	CO- 	C=O	–	〃	〃	$-(CH_2)_5-$	"
37	〃	〃	–	C=O	〃	〃	〃	"
38	〃	CH_2CH_2- 	C=O	–	〃	〃	$-(CH_2)_4-$	"
39	〃	〃	–	C=O	〃	〃	〃	"
40	〃	NO_2	C=O	–	〃	〃	$-(CH_2)_6-$	"
41	〃	〃	–	C=O	〃	〃	〃	"

tetrahydro-5H-thieno[3,2-b]azepin-5-one oxalate, melting at 155-156°C.

Example 44

2-Methyl-5-[3-(4-(2-pyrimidinyl)-1-piperazinyl)propyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one dihydrochloride, melting at 226-227°C.

Example 45

2-Propionyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one, melting at 109-111°C.

Example 46

The reaction and procedure were conducted in the same manner as in Example 17 using 2-acetyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5, 6,7,8-tetrahydro-4H-thieno(3,2-c]azepin-4-one in place of 2-acetyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno [3,2-b]azepin-5-one to give 2-ethyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate as white crystals, melting at 151-154°C.

Example 47

The reaction and procedure were conducted in the same manner as in Example 17 using 2-propionyl-5-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in place of 2-acetyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno-[3,2-b]azepin-5-one to give 2-propyl-5-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate as white crystals, melting at 123-125°C.

The following compounds can be prepared in a similar manner as the above examples.

Example 48

2-Methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one, melting at 86-88°C. Its hydrochloride melts at 197-198°C.

Example 49

4-[3-(4-(2-Pyrimidinyl)-1-piperazinyl)propyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one oxalate, melting at 171-173°C.

Example 50

5-[4-(4-(2-Pyrimidinyl)-1-piperazinyl)pentyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate, melting at 174-176°C.

Example 51

To a solution of 4.2 g of 5-(4-chlorobutyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 50 ml of toluene-dimethylformamide (1:1) were added 4.8 g of 4-[bis(4-fluorophenyl)methylene]-piperidine, 4.6 g of potassium carbonate and 2.5 g of potassium iodide, and then the mixture was stirred for 6 hours at 90°C-100°C. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated in vacuo. The resulting residue was dissolved in ethanol and to the solution was added 1.0 g of fumaric acid to produce its fumarate. The precipitated crystals were collected by filtration and recrystallized from ethanol to give 1.4 g of 5-[4-(4-(bis(4-fluorophenyl)methylene)piperidino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate as white crystals, melting at 203-204°C.

Example 52

4-[2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethyl]-4,6,7,8-tetrahydro-5H-thieno[3,2-b]azepin-5-one, melting at 212-214°C with decomposition.

Example 53

2-Methyl-5-(4-morpholinobutyl)-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 235-236°C.

Example 54

5-[4-(4-(4-fluorobenzoyl)piperidino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 238-241°C.

Example 55

5-[4-(4-(1,3-Dihydro-2-oxo-2H-benzimidazol-1-yl)piperidino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno-(3,2-c]azepin-4-one hydrochloride, melting at 259-261°C.

Example 56

To a solution of 5.0 g of 2-methyl-5,6,7,8-tetrahydro-4H-thieno-(3,2-c]azepin-4-one in 70 ml of dimethylformamide was added 4.4 g of potassium t-butoxide with stirring under ice-cooling and the mixture was stirred for an hour at room temperature. To the mixture was added 7.1 g of bromoacetaldehyde (2-bromo-1,1-diethoxyethane) dropwise under ice-cooling. The mixture was stirred at 60°C for 5 hours and poured into chilled water and then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting oil was chromatographed on a silica gel using chloroform as an eluent to give 2.5 g of 5-(2,2-diethoxyethyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c] -azepin-4-one as a pale yellow oil. To the solution of 2.1 g of 5-(2,2-diethoxyethyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one in 30 ml of tetrahydrofuran was added 10 ml of a 10% hydrochloric acid solution, and the mixture was stirred for 2 hours at room temperature, poured into water and then extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give 1.39 g of 2-methyl-5,6,7,8-tetrahydro-4-oxo-4H-thieno[3,2-c]azepin-5-acetoaldehyde. To the solution of 1.39 g of 2-methyl-5,6,7,8-tetrahydro-4-oxo-4H-thieno[3,2-c]azepin-5-acetoaldehyde in 20 ml of ethanol were added 2.4 g of 4-[bis(4-fluorophenyl)methylene]piperidine and 0.39 g of sodium cyanoborohydride. The mixture was stirred for 2.5 hours at room temperature, poured into chilled water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting orange oil was chromatographed on a silica gel using chloroform as an eluent and the eluate was concentrated under reduced pressure. The resulting residue was dissolved in ethanol and to the solution of the residue was added ethanolic hydrochloric acid to produce its hydrochloride. The precipitated crystals were collected by filtration and recrystallized from methanol to give 5-[2-(4-(bis(4-fluorophenyl)methylene)piperidino)ethyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride as white crystals, melting at 228-229°C.

Example 57

5-[4-(4-(Bis(4-fluorophenyl)methyl)-1-piperazinyl)butyl]-2-methyl-5, 6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one dimaleate 1/4hydrate, melting at 131-132°C.

Example 58

5-[4-(4-(5-Chlorobenzoxazol-2-yl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one maleate, melting at 161-162°C.

Example 59

5-[6-(4-(3-Chlorophenyl)-1-piperazinyl)hexyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one

maleate, melting at 149-150°C.

Example 60

5-[4-(4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 231-233°C.

Example 61

5-[4-(4-(3-Trifluoromethylphenyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one fumarate, melting at 179-182°C.

Example 62

5-[2-(4-(2-Methoxyphenyl)-1-piperazinyl)ethy1]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 231-233°C.

Example 63

5-[4-(4-(2,3-Dimethylphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 243-247°C.

Example 64

5-[4-(4-(2-Methoxyphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride monohydrate, melting at 207-209°C.

The compounds shown in the Tables 3, 4 and 5 can be prepared in a similar manner:

Example 93

To 300 g of polyphosphoric acid warmed at 70°C was added 19.5 g of 5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-one 4-oxime portionwise with stirring for 20 minutes. The mixture was stirred at 80°C for 2.5 hours, poured into chilled water and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting crude crystals were recrystallized from ethanol to give 10 g of 2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one as white crystals, melting at 195-196°C.

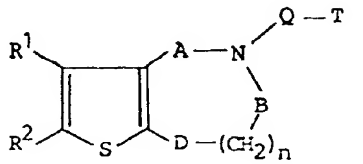
Example 94

The reaction and procedure were conducted in the same manner as in Example 93 using 5,6-dihydro-2-methyl-4H-thieno[2,3-b]thiopyran-4-one 4-oxime in place of 5,6-dihydro-4H-thieno[2,3-b]thiopyran-4-one 4-oxime to give 2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one as white crystals, melting at 155-156°C.

Example 95

From the crude product obtained by the reaction of Example 94 was removed the compound of Example 94 and the remaining mixture was purified to give 3,4-dihydro-7-methylthieno[2,3-b][1,4]thiazepin-2(1H)-

Table 3



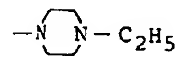
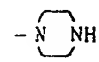
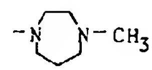
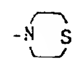
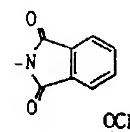
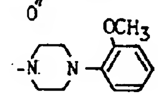
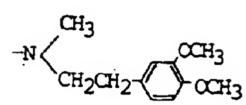
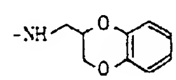
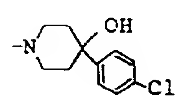
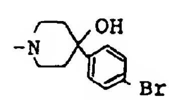
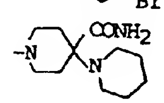
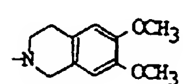
No.	R^1	R^2	A	B	D	n	Q	T
65	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
66	〃	H	〃	〃	〃	〃	〃	
67	〃	〃	〃	〃	〃	〃	〃	
68	〃	〃	〃	〃	〃	〃	〃	
69	〃	〃	〃	〃	〃	〃	〃	
70	〃	$COCH_3$	〃	〃	〃	〃	〃	
71	〃	CH_3	〃	〃	〃	〃	$-(CH_2)_3-$	
72	〃	〃	〃	〃	〃	〃	$-(CH_2)_4-$	
73	〃	H	〃	〃	〃	〃	$-(CH_2)_3-$	
74	〃	CH_3	〃	〃	〃	〃	〃	
75	〃	〃	〃	〃	〃	〃	$-(CH_2)_4-$	
76	〃	〃	〃	〃	〃	〃	〃	

Table 4

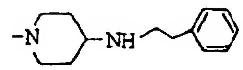
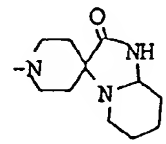
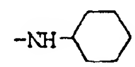
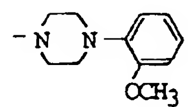
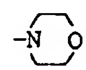
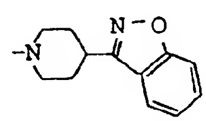
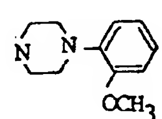
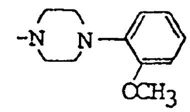
No.	R^1	R^2	A	B	D	n	Q	T
77	H	H	C=O	–	CH_2	2	$-(CH_2)_4-$	
78	〃	CH_3	〃	〃	〃	〃	〃	
79	〃	H	〃	〃	〃	〃	〃	$-N(CH_3)_2$
80	〃	CH_3	〃	〃	〃	〃	〃	
81	CH_3	〃	〃	〃	〃	〃	〃	
82	Cl	Cl	〃	〃	〃	〃	〃	〃
83	H	H	〃	〃	〃	〃	〃	
84	〃	CH_3	〃	〃	〃	〃	〃	
85	〃	〃	〃	〃	〃	〃	〃	$-NH_2$
86	〃	〃	〃	〃	〃	〃	〃	$-NH-C_4H_9$
87	〃	Br	〃	〃	〃	〃	〃	
88	〃	I	〃	〃	〃	〃	〃	〃

Table 5

No.	R^1	R^2	A	B	D	n	Q	T
89	H	C_2H_5	C=O	–	CH_2	2	$-(CH_2)_4-$	
90	〃	CHO	〃	〃	〃	〃	〃	"
91	〃	NO_2	〃	〃	〃	〃	〃	"
92	〃	H	〃	C=O	〃	1	〃	"

one as white crystals, melting at 208-210°C.

Example 96

To a solution of 4.9 g of 2,3-dihydrothieno(3,2-f]-1,4-thiazepin-5(4H)-one in 50 ml of N,N-dimethylformamide is added 3.6 g of potassium t-butoxide with stirring under ice-cooling and the mixture was stirred at room temperature for an hour and then 5.4 g of 1-bromo-4-chlorobutane was added. The mixture was stirred for 5 hours, poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting residue was chromatographed on a silica gel using chloroform and methanol (99.8:0.2) as an eluent to give 6.9 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one as pale yellow oil.

Example 97

The reaction and procedure were conducted in the same manner as in Example 96 using 2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one in place of 2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one to give 4-(4-chlorobutyl)-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one.

Example 98

The reaction and procedure were conducted in the same manner as in Example 96 using 3,4-dihydro-7-methylthieno[2,3-b][1,4]thiazepin-2(1H)-one in place of 2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one to give 1-(4-chlorobutyl)-3,4-dihydro-7-methylthieno[2,3-b][1,4]-thiazepin-2(1H)-one.

Example 99

To a suspension of 13 g of aluminum chloride in 150 ml of methylene chloride was added 4.6 ml of acetyl chloride under ice-cooling and the mixture was stirred for 15 minutes. To the mixture was added a solution of 9.0 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 20 ml of methylene chloride and the mixture was stirred at room temperature for 2 hours. Then, the mixture was poured into chilled water and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting crystals were recrystallized from ethyl acetate to give 6.9 g of 7-acetyl-4-(4-chlo-

robutyl)-2,3-dihydrothieno-[3,2-f]-1,4-thiazepin-5(4H)-one as white crystals, melting at 132-134°C.

Example 100

To a solution of 3.0 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 60 ml of acetic acid was added 1.5 ml of bromine with stirring at 60°C and the mixture was stirred for 20 minutes at the same temperature. The mixture was poured into chilled water and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting crystals were recrystallized from ethanol to give 2.0 g of 7-bromo-4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one as white crystals, melting at 81-89°C.

Example 101

To a solution of 8.0 g of 2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 160 ml of N,N-dimethylformamide was added 6.3 g of potassium t-butoxide with stirring under ice-cooling and the mixture was stirred for an hour at room temperature. Then, to the mixture was added 8.4 ml of bromoacetaldehyde diethyl acetal under ice-cooling. The mixture was stirred for 5 hours at room temperature and water was added thereto and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was chromatographed on a silica gel using and chloroform and methanol (99.8:0.2) as an eluent to give 6.9 g of 4-(2,2-diethoxyethyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one as a pale yellow oil. To the solution of thus obtained 6.7 g of 4-(2,2-diethoxyethyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 150 ml of tetrahydrofuran was added 20 ml of 10% hydrochloric acid and the mixture was allowed to stand for 20 hours at room temperature, and then poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off to give 4.4 g of 2,3,4,5-tetrahydro-5-oxothieno[3,2-f]-1,4-thiazepin-4-acetaldehyde as a pale yellow oil.

Example 102

To a solution of 3.4 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 100 ml of formic acid was added 2.9 ml of 30% hydrogen peroxide and the mixture was stirred for 3 hours at room temperature. Then, the mixture was poured into ca. 3% aqueous sodium hydrogensulfite solution and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off to give 3.5 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one 1,1-dioxide as a pale yellow oil.

Example 103

To a solution of 4.4 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 100 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 5.2 g of N-(2-pyrimidinyl)piperazine and 4.4 g of potassium carbonate and the mixture was stirred for 5 hours at 80°C. Then, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was chromatographed on a silica gel using chloroform and methanol (95:5) as an eluent and the resulting oil was dissolved in ethanol. To the solution was added fumaric acid to form fumarate and the precipitated crystals were recrystallized from ethanol to give 2.5 g of 2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one fumarate as white crystals, melting at 205-210°C.

Example 104

The reaction and procedure were conducted in the same manner as in Example 103 using N-(3-trifluoromethylphenyl)piperazine in place of N-(2-pyrimidinyl)piperazine to give 4-[4-(4-(3-trifluoromethylphenyl)-1-piperazinyl)butyl]-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one fumarate as white crystals, melting at 205-206°C.

Example 105

The reaction and procedure were conducted in the same manner as in Example 103 using N-(2-methoxyphenyl)piperazine in place of N-(2-pyrimidinyl)piperazine and using hydrochloric acid in place of fumaric acid

to give 2,3-dihydro-4-[4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one hydrochloride 1/2hydrate as white crystals, melting at 211-212°C.

Example 106

The reaction and procedure were conducted in the same manner as in Example 103 using N-(1,2-benzisothiazol-3-yl)piperazine in place of N-(2-pyrimidinyl)piperazine and using hydrochloric acid in place of fumaric acid to give 4-[4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)-butyl]-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one hydrochloride as white crystals, melting at 231-233°C.

Example 107

To a solution of 2.0 g of 7-bromo-4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 40 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 1.9 g of N-(2-pyrimidinyl)piperazine dihydrochloride, 3.0 g of potassium carbonate and 1.3 g of potassium iodide and the mixture was stirred for 5 hours at 80°C. Then, the resultant mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was dissolved in ethanol and to the solution was added fumaric acid to form its fumarate. The precipitated crystals were recrystallized from ethanol to give 2.5 g of 7-bromo-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one fumarate 1/2 hydrate as white crystals, melting at 169-170°C.

Example 108

To a solution of 2.0 g of 4-(4-chlorobutyl)-2,3-dihydro-7-methyl-thieno[3,2-f]-1,4-thiazepin-5(4H)-one in 30 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 2.2 g of N-(2-methoxyphenyl)piperazine hydrochloride, 3.0 g of potassium carbonate and 0.5 g of potassium iodide and the mixture was stirred for 3 hours at 80°C. Then, the resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was dissolved in ethanol and to the solution was added oxalic acid to form its oxalate. The precipitated crystals were recrystallized from methanol to give 2.5 g of 2,3-dihydro-4-[4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl]-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one oxalate monohydrate as white crystals, melting at 128-130°C.

Example 109

The reaction and procedure were conducted in the same manner as in Example 108 using N-[bis(4-fluorophenyl)methyl)piperazine in place of N-(2-methoxyphenyl)piperazine and using maleic acid in place of oxalic acid to give 4-[4-(4-(bis(4-fluorophenyl)methyl-1-piperazinyl)-butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one dimaleate 1/4hydrate as white crystals, melting at 165-166°C.

Example 110

The reaction and procedure were conducted in the same manner as in Example 108 using N-(diphenylmethyl)piperazine in place of N-(2-methoxyphenyl)piperazine and using maleic acid in place of oxalic acid to give 2,3-dihydro-7-methyl-4-[4-(4-diphenylmethyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one dimaleate as white crystals, melting at 166-168°C.

Example 111

The reaction and procedure were conducted in the same manner as in Example 108 using N-(3-trifluoromethylphenyl)piperazine in place of N-(2-methoxyphenyl)piperazine to give 4-[4-(4-(3-trifluoromethyl-phenyl)-1-piperazinyl)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one oxalate as white crystals, melting at 135-137°C.

Example 112

The reaction and procedure were conducted in the same manner as in Example 108 using N-(2-pyrimidinyl)piperazine in place of N-(2-methoxyphenyl)piperazine and using fumaric acid in place of oxalic acid to give 2,3-dihydro-7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one fumarate as

white crystals, melting at 196-198°C.

Example 113

The reaction and procedure were conducted in the same manner as in Example 108 using N-(hexadecyl) piperazine in place of N-(2-methoxyphenyl)piperazine and using hydrochloric acid in place of oxalic acid to give 4-[4-(4-hexadecyl)-1-piperazinyl)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one dihydrochloride 1/2hydrate as white crystals, melting at 157-159°C with decomposition.

Example 114

The reaction and procedure were conducted in the same manner as in Example 108 using N-(5-chloro-1,3-benzoxazol-2-yl)piperazine in place of N-(2-methoxyphenyl)piperazine and using maleic acid in place of oxalic acid to give 4-[4-(4-(5-chloro-1,3-benzoxazol-2-yl)-1-piperazinyl)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate as white crystals, melting at 188-189°C.

Example 115

The reaction and procedure were conducted in the same manner as in Example 108 using N-[(4-chlorophenyl)phenylmethyl)piperazine in place of N-(2-methoxyphenyl)piperazine and using maleic acid in place of oxalic acid to give 4-[4-(4-(4-chlorophenyl)phenylmethyl)-1-piperazinyl)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate as white crystals, melting at 157-159°C.

Example 116

To a solution of 2.0 g of 4-(6-chlorohexyl)-2,3-dihydro-7-methyl-thieno[3,2-f]-1,4-thiazepin-5(4H)-one in 80 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 3.1 g of N-(2-pyrimidinyl)piperazine dihydrochloride, 3.0 g of potassium carbonate and 0.5 g of potassium iodide and the mixture was stirred for 3 hours at 80°C. Then, the resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The residue was dissolved in ethanol and to the solution is added oxalic acid to form its oxalate. The precipitated crystals are recrystallized from methanol to give 1.3 g of 2,3-dihydro-7-methyl-4-[6-(4-(2-pyrimidinyl)-1-piperazinyl)hexyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one oxalate monohydrate as white crystals, melting at 161-162°C.

Example 117

To a solution of 6.8 g of 7-acetyl-4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one in 80 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 5.3 g of N-(2-pyrimidinyl)piperazine dihydrochloride, 6.2 g of potassium carbonate and 3.6 g of potassium iodide and the mixture was stirred for 8 hours at 80°C. Then, the resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting crude crystals were recrystallized from isopropyl alcohol to give 9.4 g of 7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one as white crystals, melting at 118-120°C.

Example 118

To a solution of 3.9 g of 2,3-dihydro-7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one in 60 ml of acetic acid was added a solution of 2.5 g of sodium metaperiodate in 10 ml of water with stirring at room temperature and the mixture was stirred for 2.5 hours. Then, the mixture was poured into chilled water, made alkaline with potassium carbonate and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting residue was dissolved in isopropyl alcohol and to the solution was added hydrochloric acid to form hydrochloride. The precipitated crystals were recrystallized from ethanol to give 2.7 g of 2,3-dihydro-7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-thieno[3,2-f]-1,4-thiazepin-5(4H)-one 1-oxide hydrochloride as white crystals, melting at 250-252°C with decomposition.

Example 119

To a solution of 2.0 g of 7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one in 20 ml of acetic acid was added 1.0 g of 30% hydrogen peroxide and the mixture was stirred for 20 hours at room temperature. Then, the mixture was poured into ca. 3% aqueous sodium hydrogen sulfite solution and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting crude crystals were recrystallized from ethanol to give 1.5 g of 7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one 1-oxide as white crystals, melting at 103-106°C.

Example 120

To a solution of 4.1 g of 4-(4-chlorobutyl)-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one 1,1-dioxide in 80 ml of a mixed solvent of N,N-dimethylformamide and toluene (1:1) were added 3.2 g of N-(2-pyrimidinyl)piperazine dihydrochloride, 3.8 g of potassium carbonate and 2.3 g of potassium iodide and the mixture was stirred for 3 hours at 90°C. Then, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting residue was chromatographed on a silica gel and eluted using chloroform and methanol (95:5) as an eluent. The resulting crystals were recrystallized from ethanol to give 3.0 g of 2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one 1,1-dioxide as white crystals, melting at 161-163°C.

Example 121

To a solution of 3.5 g of 7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one in 35 ml of trifluoroacetic acid was added 2.9 ml of triethylsilane and the mixture was stirred for 20 hours at room temperature. Then, the mixture was poured into water, made alkaline with potassium carbonate and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was distilled off. The resulting residue was dissolved in ethanol and to the solution was added hydrochloric acid to form hydrochloride. The precipitated crystals were recrystallized from ethanol to give 2.0 g of 7-ethyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno-[3,2-f]-1,4-thiazepin-5(4H)-one hydrochloride 3/2hydrate as white crystals, melting at 207-209°C.

Example 122

4-[2-(4-(Bis(4-fluorophenyl)methylene)piperidino)ethyl]-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-5(4H)-one fumalate, melting at 205-207°C.

Example 123

4-[4-(4-(Bis(4-fluorophenyl)methylene)piperidino)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate hydrate, melting at 96-98°C.

Example 124

4-[4-(4-(4-Fluorobenzoyl)piperidino)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one fumalate, melting at 184-185°C.

Example 125

2,3-Dihydro-7-methyl-4-(4-morpholinobutyl)thieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate, melting at 196-197°C.

Example 126

2,3-Dihydro-4-[4-(N-(2-(3,4-dimethoxyphenyl)ethyl)-N-methylamino)-butyl]-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one fumalate, melting at 151-153°C.

Example 127

2,3-Dihydro-7-methyl-4-(4-piperidinobutyl)thieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate, melting at 158-159°C.

Example 128

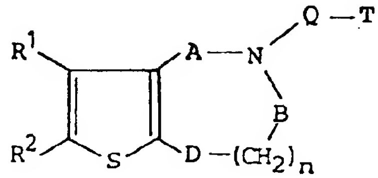
4,5,6,7-Tetrahydro-7-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-8H-thieno[2,3-c]azepin-8-one maleate, melting at 164-167°C.

The compounds shown in the Tables 6 and 7 can be prepared in a similar manner.

Example 153

2,3-Dihydro-7-methyl-4-[4-(2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo-[1,2-a]pyridine-3-spiro-4′-piperidino)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate monohydrate, melting at 210-211°C.

Table 6



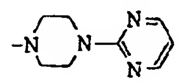
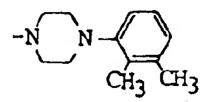
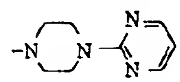
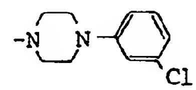
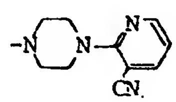
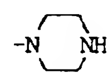
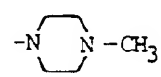
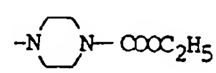
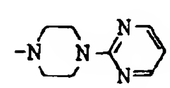
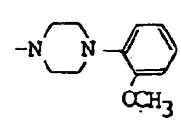
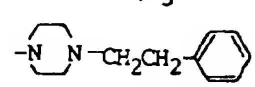
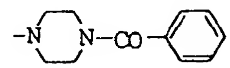
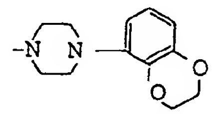
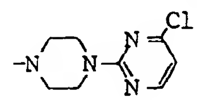
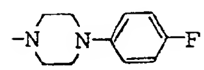
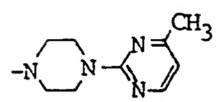
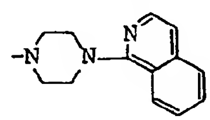
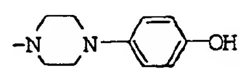
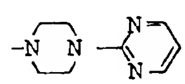
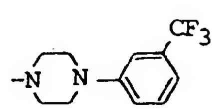
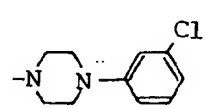
No.	R^1	R^2	A	B	D	n	Q	T
129	H	$COCH_3$	C=O	–	S	2	$-(CH_2)_3-$	
130	″	CH_3	″	″	″	″	$-(CH_2)_4-$	
131	″	$CH(OH)CH_3$	″	″	″	″	″	
132	″	CH_3	″	″	″	″	$-(CH_2)_3-C(CH_3)_2-$	″
133	″	″	″	″	″	″	$-(CH_2)_4-$	
134	″	″	″	″	″	″	″	
135	″	″	″	″	″	″	″	
136	″	″	″	″	″	″	″	
137	″	″	″	″	″	″	″	
138	″	$SO_2N(CH_3)_2$	″	″	″	″	″	
139	″	$COCH_3$	″	″	″	″	$-(CH_2)_2-$	
140	″	CH_3	″	″	″	″	$-(CH_2)_4-$	

Table 7

No.	R^1	R^2	A	B	D	n	Q	T
141	H	CH_3	C=O	–	S	2	$-(CH_2)_4-$	
142	〃	〃	〃	〃	〃	〃	〃	
143	〃	〃	〃	〃	〃	〃	〃	
144	〃	〃	〃	〃	〃	〃	〃	
145	〃	〃	〃	〃	〃	〃	〃	
146	〃	〃	〃	〃	〃	〃	〃	
147	〃	〃	〃	〃	〃	〃	〃	
148	〃	〃	–	C=O	〃	〃	〃	
149	〃	〃	C=O	〃	〃	1	〃	"
150	〃	〃	〃	〃	SO	〃	〃	"
151	〃	〃	〃	〃	S	〃	〃	
152	〃	〃	〃	〃	〃	〃	〃	

Example 154

2-Methyl-5-[4-(4-(2-pyridyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one 3/2maleate, melting at 167-169°C.

Example 155

2-(1-Hydroxyethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one maleate, melting at 159-160°C.

Example 156

4-[3-(4-(Bis(4-fluorophenyl)methyl-1-piperazinyl)propyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one, melting at 100-102°C.

Example 157

4-(4-Aminobutyl)-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one hydrochloride 1/4hydrate, melting at 171-172°C.

Example 158

4-[4-(1,2,3,4-Tetrahydro-6,7-dimethoxy-2-isoquinolyl)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one maleate 1/4hydrate, melting at 153-154°C.

Example 159

4-[3-(4-(2-Methoxyphenyl)-1-piperazinyl)propyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one dihydrochloride 1/2hydrate, melting at 203-205°C.

Example 160

5-[4-(4-(Bis(4-fluorophenyl)methyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one dimaleate, melting at 125-126°C.

Example 161

2-Methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-thione hydrochloride 3/2hydrate, melting at 235°C.

Example 162

7-Methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydrothieno[3,2-f]-1,4-thiazepin-3(4H)-one fumalate, melting at 190-192°C.

Example 163

5-[4-((1,4-Benzodioxan-2-yl)methylamino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 189-192°C.

Example 164

To a solution of 2.0 g of 6,7,8,9-tetrahydrothieno[3,2-b]azocin-5(4H)-one in 20 ml of dimethylformamide was added 1.3 g of potassium t-butoxide under ice-cooling and stirred at the same temperature. To the mixture was added 2.0 g of 1-bromo-4-chlorobutane and stirred at room temperature for 5 hours. The mixture was poured into water and extracted ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on a silica gel using a chloroform as an eluent to give 2.8 g of 4-(4-chlorobutyl)-6,7,8,9-tetrahydrothieno[3,2-b]azocin-5(4H)-one as a pale yellow

oil.

Example 165

The reaction and procedure are conducted in the same manner as in Example 164 using 6,7,8,9-tetrahydrothieno[3,2-c]azocin-4(5H)-one in place of 6,7,8,9-tetrahydrothieno[3,2-b]azocin-5(4H)-one to give 4-(4-chlorobutyl)-6,7,8,9-tetrahydrothieno[3,2-c]azocin-4(5H)-one.

Example 166

To a solution of 2.8 g of 4-(4-chlorobutyl)-6,7,8,9-tetrahydrothieno[3,2-b]azocin-5(4H)-one in a mixed solvent of dimethylformamide (20 ml) and toluene (20 ml) were added 2.6 g of 2-pyrimidinyl-1-piperazine dihydrochloride, 4.3 g of potassium carbonate and 1.7 g of potassium iodide and stirred at 80°C for 3 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried and concentrated under reduced pressure. The resulting crystals were recrystallized from ethyl acetate to give 1.2 g of 6,7,8,9-tetrahydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-b]azocin-5(4H)-one as white crystals, melting at 108-112°C.

Example 167

The reaction and procedure were conducted in the same manner as in Example 166 using 4-(4-chlorobutyl)-6,7,8,9-tetrahydrothieno[3,2-c]azocin-4(5H)-one in place of 4-(4-chlorobutyl)-6,7,8,9-tetrahydrothieno[3,2-b]azocin-5(4H)-one and the obtained pale yellow oil was dissolved in ethanol. To the solution was added isopropyl alcohol-hydrochloric acid and the precipitated crystals were recrystallized from ethanol to give 6,7,8,9-tetrahydro-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-c]azocin-4(5H)-one hydrochloride 1/2 hydrate as white crystals, melting at 217-222°C with decomposition.

Example 168

To a suspension of 6.0 g of 2-acetyl-5,6,7,8-tetrahydro-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4H-thieno[3,2-c]azepin-4-one maleate in 100 ml of ethanol were added 0.92 g of hydroxylamine hydrochloride and 4.0 g of sodium hydrogencarbonate with stirring and the mixture was refluxed for 5 hours. After cooling, the mixture was concentrated under reduced pressure, to the residue was added water and the solution was extracted with chloroform. The extract was washed with water, dried and concentrated in vacuo. The resulting crystals were recrystallized from a mixed solvent of ethanol and isopropyl ether to give 4.95 g of 5,6,7,8-tetrahydro-2-(1-(hydroxyimino)ethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-4H-thieno[3,2-c]azepin-4-one as white crystals, melting at 144-146°C.

Example 169

To 30 g of 115% polyphosphoric acid was added 2.4 g of 5,6,7,8-tetrahydro-2-(1-(hydroxyimino)ethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4H-thieno[3,2-c]azepin-4-one with stirring at 70°C. The mixture was stirred at the same temperature for 3 hours, poured into chilled water and made to be alkaline solution with potassium carbonate. The precipitated crystals were collected by filtration, dried and chromatographed on a silica gel using chloroform-methanol (95:5) as an eluent. The resulting crystals were recrystallized from ethyl acetate to give 0.65 g of 2-acetylamino-5,6,7,8-tetrahydro-5[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4H-thieno[3,2-c]azepin-4-one as white crystals, melting at 158-161°C.

Example 170

To a suspension of 1.0 g of 5-[4-((1,4-benzodioxan-2-ylmethyl)-amino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride in 15 ml of ethanol was added 0.4 ml of formalin and then added 0.3 g of sodium cyanoborohydride with stirring at room temperature. The mixture was stirred at the same temperature for 2 hours, concentrated under reduced pressure and to the residue was added water, and then extracted with chloroform. The extract was washed with water, dried and concentrated in vacuo. The resulting oil was treated to form hydrochloride by a conventional method. The precipitated crystals were recrystallized from a mixed solvent of isopropyl alcohol and ethyl acetate to give 0.7 g of 5-[4-(N-(1,4-benzodioxan-2-ylmethyl)-N-methylamino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride 1/4hydrate as

white crystals, melting at 193-195°C.

Example 171

To a solution of 5.0 g of 5,6,7,8-tetrahydro-2-methyl-4H-thieno-[3,2-c]azepin-4-one in 70 ml of dimethylformamide was added 6.8 g of potassium t-butoxide under ice-cooling and stirred at room temperature for an hour. Then, to the mixture was added 4.4 g of dimethylaminoethylchloride hydrochloride and stirred at 60°C for 5 hours. After cooling, to the mixture was added water and the solution was extracted with ethyl acetate. The extract was washed with water, dried and concentrated under reduced pressure. The resulting oil was treated to form hydrochloride by a conventional method. The precipitated crystals were recrystallized from a mixed solvent of ethanol and ethyl acetate to give 4.0 g of 5-(2-dimethylaminoethyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride as white crystals, melting at 229-231°c.

Example 172

To a solution of 0.9 g of 5-(2-dimethylaminoethyl)-2-methyl-5,6,7,8-tetrahydro-4H-thieno(3,2-c]azepin-4-one in 30 ml of acetone was added 0.4 ml of methyl iodide at room temperature. After being allowed to stand 30 minutes, the precipitated crystals were collected by filtration and washed with acetone to give 1.1 g of N-(2-(5,6,7,8-tetrahydro-2-methyl-4-oxo-4H-thieno(3,2-c]azepin-5-yl)ethyl]-N,N-dimethylammonium iodide as white crystals, melting at 237-239°c.

Example 173

To a suspension of 0.5 g of N-(2-(5,6,7,8-tetrahydro-2-methyl-4-oxo-4H-thieno(3,2-c]azepin-5-yl)ethyl]-N,N-dimethylammonium iodide in 20 ml of 1,3-dimethyl-2-imidazolidinone was added 0.52 g of 2-pyrimidinyl-1-piperazine and stirred at 130°C for 4 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried and concentrated in vacuo. The residue was chromatographed on a silica gel using chloroform-ethanol (97:3) as an eluent. The resulting crystals were recrystallized from a mixed solvent of ethyl acetate and isopropyl ether to give 0.2 g of 2-methyl-5-(2-(4-(2-pyrimidinyl)-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-4H-thieno(3,2-c]azepin-4-one as pale brown crystals, melting at 137-139°C.

Example 174

To a solution of 5.0 g of 5-(4-chlorobutyl)-5,6,7,8-tetrahydro-2-methyl-4H-thieno[3,2-c]azepin-4-one in 60 ml of acetic acid was added 1.9 ml of bromine at 60°C and stirred for 20 minutes. After cooling, to the mixture was added an aqueous saturated sodium thiosulfate solution and the mixture was neutralized with potassium carbonate, and then extracted with ethyl acetate. The extract was washed with water, dried and concentrated under reduced pressure. The resulting crude crystals were recrystallized from a mixed solvent of isopropyl alcohol and hexane to give 2.3 g of 3-bromo-5-(4-chlorobutyl)-5,6,7,8-tetrahydro-2-methyl-4H-thieno[3,2-c]azepin-4-one as pale yellow crystals, melting at 78-80°C.

Example 175

To a solution of 2.2 g of 3-bromo-5-(4-chlorobutyl)-5,6,7,8-tetrahydro-2-methyl-4H-thieno[3,2-c]azepin-4-one in 50 ml of dimethylformamide-toluene (1:1) were added 1.6 g of 2-pyrimidinyl-1-piperazine dihydrochloride, 1.9 g of potassium carbonate and 1.2 g of potassium iodide and stirred at 80-90°C for 3 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried and concentrated under reduced pressure. The residue was treated to form hydrochloride by a conventional method. The precipitated crystals were recrystallized from a mixed solvent of isopropyl alcohol and acetone to give 1.2 g of 3-bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-2-methyl-4H-thieno[3,2-c]azepin-4-one hydrochloride 1/2hydrate as white crystals, melting at 209-213°C.

Example 176

To a solution of 3.0 g of 4-(4-chlorobutyl)-2,3-dihydro-7-methyl-thieno[3,2-f][1,4]thiazepin-5(4H)-one in 30 ml of dimethylformamide was added 2.3 g of potassium phthalimide and stirred at 70-80°C for 6 hours. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water,

dried and concentrated in vacuo. The resulting crude crystals were recrystallized from methanol to give 4.6 g of 4-(4-phthalimidobutyl)-2,3-dihydro-7-methylthieno[3,2-f][1,4]thiazepin-5(4H)-one hydrate as white crystals, melting at 120-121°C.

Example 177

To a suspension of 4.0 g of 7-methyl-4-(4-phthalimidobutyl)-2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one in 40 ml of ethanol was added 1.5 ml of hydrazine hydrate and the mixture was refluxed under heating for 5 hours. After cooling, the precipitated crystals were filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel using chloroform-methanol (10:1) as an eluent. The resulting oil was treated to form hydrochloride by a conventional method and recrystallized from methanol to give 0.62 g of 4-(4-aminobutyl)-7-methyl-2,3-dihydrothieno[3,2-f][1,4]thiazepin-5(4H)-one hydrochloride 1/4hydrate as white crystals, melting at 171-172°C.

Example 178

5-[4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one hydrochloride, melting at 238-241°C.

Example 179

5-[6-(4-Bis(4-fluorophenyl)methyl-1-piperazinyl)hexyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one dimaleate 1/2hydrate, melting at 106-108°C.

Example 180

4-[3-(4-(4-Chlorophenyl)-4-hydroxypiperidino)propyl]-2,3-dihydro-7-methylthieno[3,2-f][1,4]thiazepin-5 (4H)-one, melting at 144-145°C.

Example 181

4-[4-(4-(4-Chlorophenyl)-4-hydroxypiperidino)butyl]-2,3-dihydro-7-methylthieno[3,2-f][1,4]thiazepin-5(4H)-one hydrochloride, melting at 254-255°C.

Example 182

3-Acetyl-2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one dioxalate, melting at 158-159°C.

Example 183

1,3-Dimethyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4,6,7,8-tetrahydro-5H-thieno[3,4-b]azepin-5-one hydrochloride, melting at 232-234°C.

Example 184

Methyl 2-methyl-5,6,7,8-tetrahydro-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-4-oxo-4H-thieno[3,2-c]azepine-3-carboxylate

Example 185

2-Methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepine-4,6-dione

Example 186

2-Methyl-5-[4-(4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepine-4,6-dione

Example 187

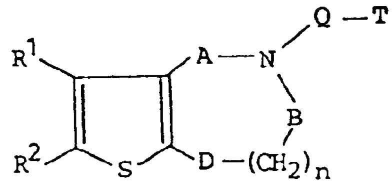
7-Methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydro-4H-thieno[3,2-f][1,4]thiazepine-3,5-dione

Example 188

4-[4-(4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydro-7-methyl-4H-thieno[3,2-f][1,4]thiazepine-3,5-dione

The compounds shown in the Tables 8 to 31 can be prepared in a similar manner.

Table 8



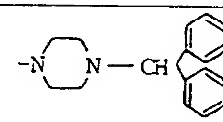
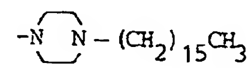
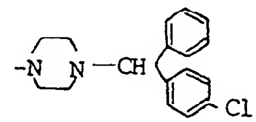
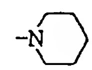
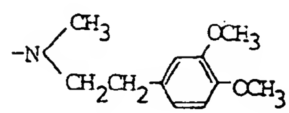
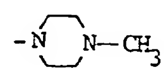
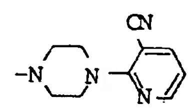
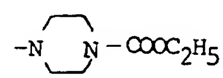
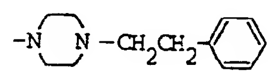
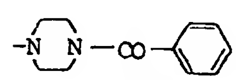
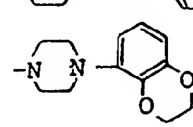
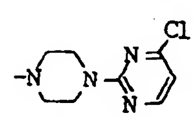
No.	R^1	R^2	A	B	D	n	Q	T
201	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
202	〃	〃	〃	〃	〃	〃	〃	
203	〃	Br	〃	〃	〃	〃	$-(CH_2)_3-CH(CH_3)-$	
204	〃	〃	〃	〃	〃	〃	〃	
205	〃	$COCH_3$	〃	〃	〃	〃	$-(CH_2)_6-$	
206	〃	〃	〃	〃	〃	〃	〃	
207	〃	〃	〃	〃	〃	〃	〃	
208	〃	C_3H_7	〃	〃	〃	〃	$-(CH_2)_4-$	
209	CH_3	CH_3	〃	〃	〃	〃	〃	
210	〃	〃	〃	〃	〃	〃	〃	
211	H	〃	〃	〃	〃	〃	〃	
212	〃	〃	〃	〃	〃	〃	〃	

Table 9

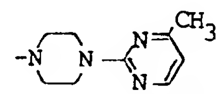
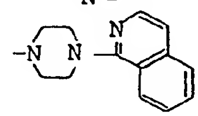
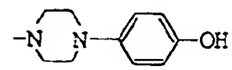
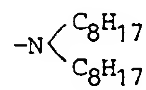
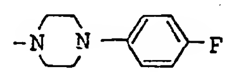
No.	R^1	R^2	A	B	D	n	Q	T
213	H	NO_2	C=O	–	CH_2	2	$-(CH_2)_4-$	
214	〃	CH_3	〃	〃	〃	〃	〃	
215	〃	〃	〃	〃	〃	〃	〃	
216	〃	SCH_3	〃	〃	〃	〃	〃	
217	〃	〃	〃	〃	〃	〃	〃	

Table 10

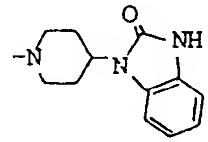
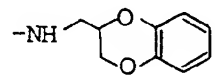
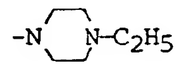
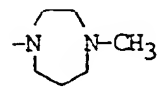
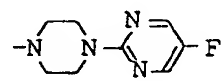
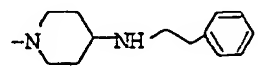
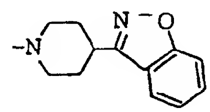
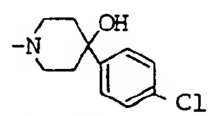
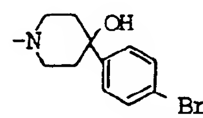
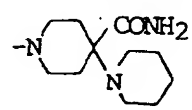
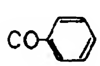
No.	R^1	R^2	A	B	D	n	Q	T
218	H	CH_3	C=O	–	S	2	$-(CH_2)_4-$	
219	〃	〃	〃	〃	〃	〃	〃	
220	〃	Br	〃	〃	〃	〃	〃	
221	〃	〃	〃	〃	〃	〃	〃	
222	〃	〃	〃	〃	SO	〃	〃	
223	〃	〃	〃	〃	〃	〃	$-(CH_2)_2-$	
224	Cl	Cl	〃	〃	〃	〃	$-(CH_2)_6-$	
225	H	〃	〃	〃	S	〃	〃	
226	〃	CH_3	〃	〃	〃	〃	〃	
227	〃	〃	〃	〃	〃	〃	$-(CH_2)_4-$	
228	〃		〃	〃	〃	〃	〃	$-N(C_3H_7)_2$
229	〃	〃	〃	〃	〃	〃	〃	$-NH_2$

Table 11

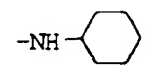
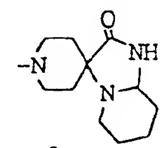
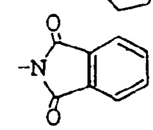
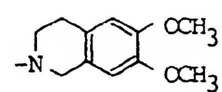
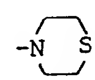
No.	R[1]	R[2]	A	B	D	n	Q	T
230	H	CH_3	C=O	–	S	2	$-(CH_2)_4-$	$-NH-C_4H_9$
231	〃	〃	〃	〃	〃	〃	〃	
232	〃	C_2H_5	〃	〃	〃	〃	〃	$-N\langle^{C_8H_{17}}_{C_8H_{17}}$
233	〃	〃	〃	〃	〃	〃	〃	
234	〃	C_3H_7	〃	〃	〃	〃	〃	
235	〃	〃	〃	〃	〃	〃	〃	
236	H	I	〃	〃	〃	〃	〃	

Table 12

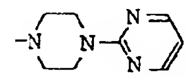
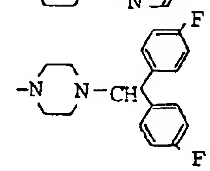
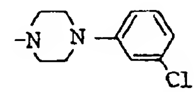
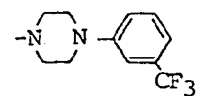
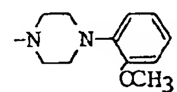
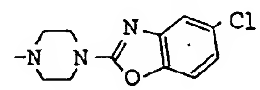
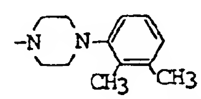
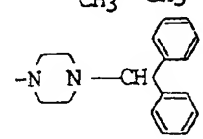
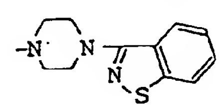
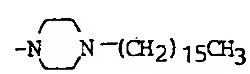
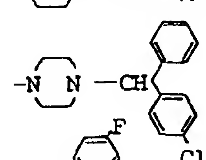
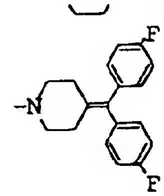
No.	R^1	R^2	A	B	D	n	Q	T
237	H	CH_3	–	C=O	CH_2	2	$-(CH_2)_4-$	
238	〃	〃	〃	〃	〃	〃	〃	
239	〃	Br	〃	〃	〃	〃	〃	
240	〃	〃	〃	〃	〃	〃	〃	
241	〃	Cl	〃	〃	〃	〃	〃	
242	〃	CH_3	〃	〃	〃	〃	〃	
243	〃	〃	〃	〃	〃	〃	〃	
244	〃	$COCH_3$	〃	〃	〃	〃	〃	
245	〃	〃	〃	〃	〃	〃	〃	
246	〃	Br	〃	〃	〃	〃	〃	
247	〃	CH_3	〃	〃	〃	〃	〃	
248	CH_3	〃	〃	〃	〃	〃	〃	

Table 13

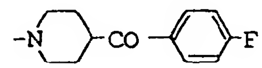
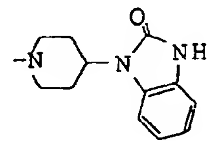
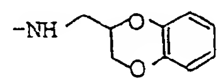
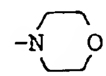
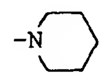
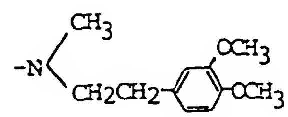
No.	R^1	R^2	A	B	D	n	Q	T
249	H	CH_3	–	C=O	CH_2	2	$-(CH_2)_4-$	
250	〃	〃	〃	〃	〃	〃	〃	
251	〃	Br	〃	〃	〃	〃	〃	
252	〃	C_2H_5	〃	〃	〃	〃	〃	
253	〃	〃	〃	〃	〃	〃	〃	
254	〃	CH_3	〃	〃	〃	〃	〃	

Table 14

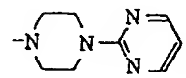
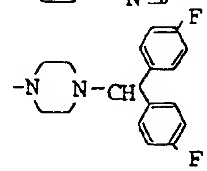
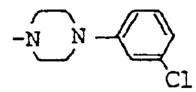
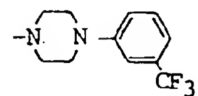
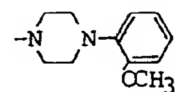
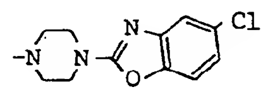
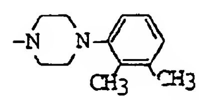
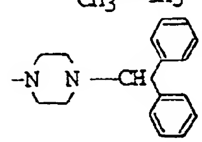
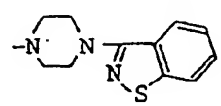
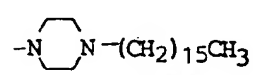
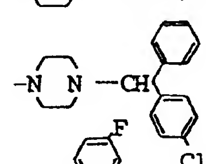
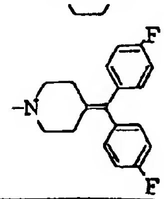
No.	R^1	R^2	A	B	D	n	Q	T
255	H	CH_3	–	C=O	S	2	$-(CH_2)_4-$	
256	〃	〃	〃	〃	〃	〃	〃	
257	〃	〃	〃	〃	〃	〃	〃	
258	〃	〃	〃	〃	〃	〃	〃	
259	〃	SO_2NH_2	〃	〃	〃	〃	〃	
260	〃	Cl	〃	〃	〃	〃	〃	
261	〃	$COCH_3$	〃	〃	〃	〃	〃	
262	〃	〃	〃	〃	SO	〃	〃	
263	〃	CH_3	〃	〃	S	〃	〃	
264	〃	H	〃	〃	〃	〃	〃	
265	〃	CH_3	〃	〃	〃	〃	〃	
266	〃	Br	〃	〃	〃	〃	〃	

Table 15

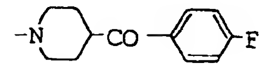
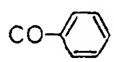
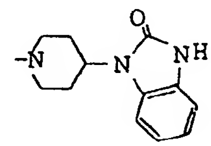
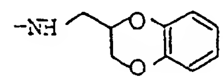
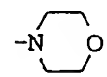
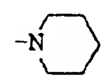
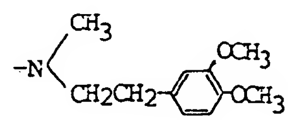
No.	R^1	R^2	A	B	D	n	Q	T
267	H	Br	–	C=O	S	2	$-(CH_2)_4-$	
268	〃		〃	〃	〃	〃	〃	
269	〃	CHO	〃	〃	〃	〃	〃	
270	〃	C_2H_5	〃	〃	〃	〃	〃	
271	〃	CH_3	〃	〃	〃	〃	〃	
272	〃	〃	〃	〃	〃	〃	〃	

Table 16

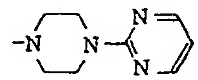
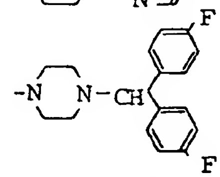
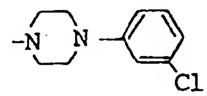
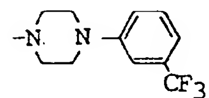
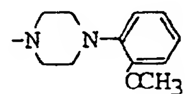
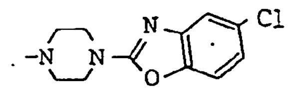
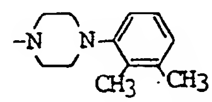
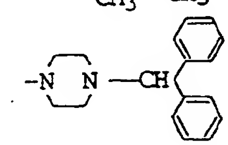
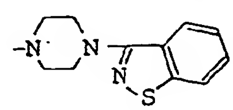
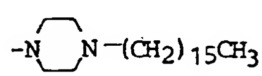
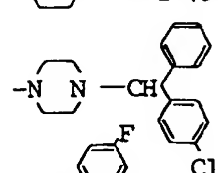
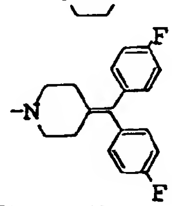
No.	R^1	R^2	A	B	D	n	Q	T
273	H	CH_3	C=O	C=O	CH_2	1	$-(CH_2)_4-$	
274	″	C_2H_5	″	″	″	″	″	
275	″	CHO	″	″	″	″	″	
276	″	Cl	″	″	″	″	″	
277	″	″	″	″	″	″	″	
278	″	C_2H_5	″	″	″	″	″	
279	″	CH_3	″	″	″	″	″	
280	″	H	″	″	″	″	″	
281	″	SO_2CH_3	″	″	″	″	″	
282	″	″	″	″	″	″	″	
283	″	CH_3	″	″	″	″	″	
284	″	CHO	″	″	″	″	″	

Table 17

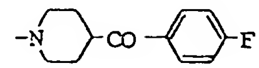
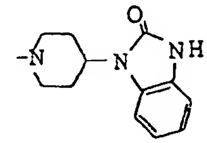
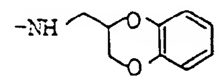
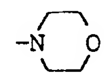
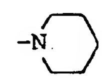
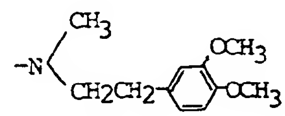
No.	R^1	R^2	A	B	D	n	Q	T
285	H	$COCH_3$	C=O	C=O	CH_2	1	$-(CH_2)_4-$	
286	〃	SO_2NH_2	〃	〃	〃	〃	〃	
287	〃	Br	〃	〃	〃	〃	〃	
288	〃	CH_3	〃	〃	〃	〃	〃	
289	〃	〃	〃	〃	〃	〃	〃	
290	〃	〃	〃	〃	〃	〃	〃	

Table 18

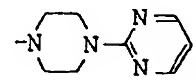
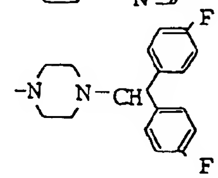
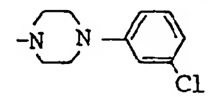
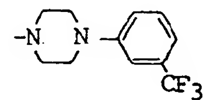
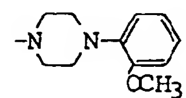
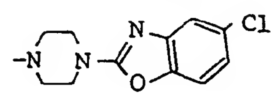
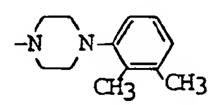
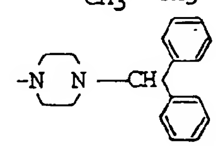
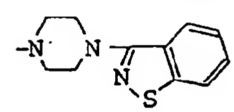
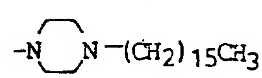
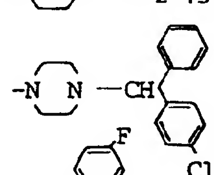
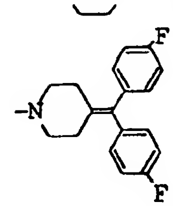
No.	R^1	R^2	A	B	D	n	Q	T
291	H	CH_3	C=O	C=O	S	1	$-(CH_2)_4-$	
292	〃	CHO	〃	〃	〃	〃	〃	
293	〃	$COCH_3$	〃	〃	〃	〃	〃	
294	〃	〃	〃	〃	〃	〃	〃	
295	〃	〃	〃	〃	〃	〃	〃	
296	〃	Cl	〃	〃	〃	〃	〃	
297	〃	CH_3	〃	〃	〃	〃	〃	
298	〃	〃	〃	〃	〃	〃	〃	
299	〃	SCH_3	〃	〃	〃	〃	〃	
300	〃	〃	〃	〃	〃	〃	〃	
301	〃	〃	〃	〃	〃	〃	〃	
302	〃	C_2H_5	〃	〃	〃	〃	〃	

Table 19

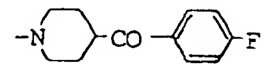
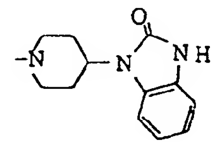
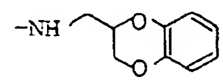
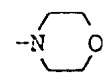
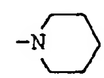
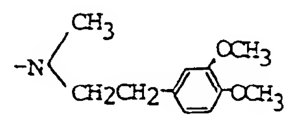
No.	R^1	R^2	A	B	D	n	Q	T
303	H	CH_3	C=O	C=O	S	1	$-(CH_2)_4-$	
304	〃	〃	〃	〃	〃	〃	〃	
305	〃	$SO_2N(CH_3)_2$	〃	〃	〃	〃	〃	
306	〃	$COCH_3$	〃	〃	〃	〃	〃	
307	〃	〃	〃	〃	〃	〃	〃	
308	〃	〃	〃	〃	〃	〃	〃	

Table 20

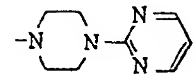
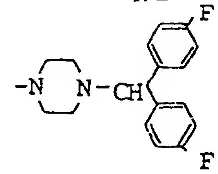
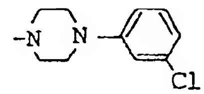
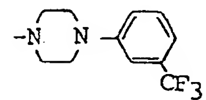
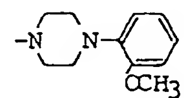
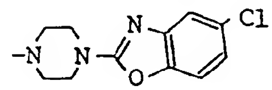
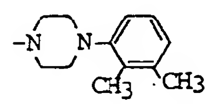
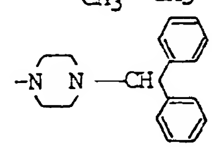
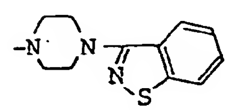
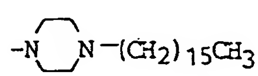
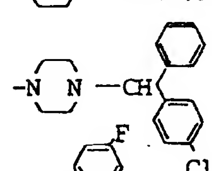
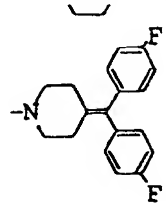
No.	R^1	R^2	A	B	D	n	Q	T
309	H	CH_3	—	C=O	CH_2	3	$-(CH_2)_4-$	
310	〃	〃	〃	〃	〃	〃	〃	
311	〃	CHO	〃	〃	〃	〃	〃	
312	〃	Br	〃	〃	〃	〃	〃	
313	〃	〃	〃	〃	〃	〃	〃	
314	〃	Cl	〃	〃	〃	〃	〃	
315	〃	$COCH_3$	〃	〃	〃	〃	〃	
316	〃	$SO_2N(CH_3)_2$	〃	〃	〃	〃	〃	
317	〃	C_2H_5	〃	〃	〃	〃	〃	
318	〃	CH_3	〃	〃	〃	〃	〃	
319	〃	〃	〃	〃	〃	〃	〃	
320	〃	〃	〃	〃	〃	〃	〃	

Table 21

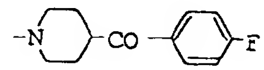
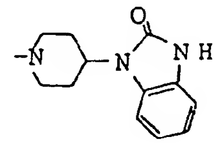
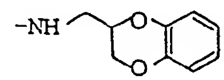
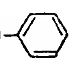
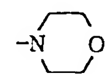
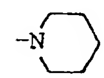
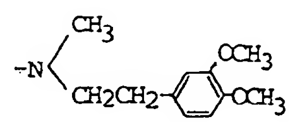
No.	R^1	R^2	A	B	D	n	Q	T
321	H	CH_3	–	C=O	CH_2	3	$-(CH_2)_4-$	
322	〃	H	〃	〃	〃	〃	〃	
323	〃	C_2H_5	〃	〃	〃	〃	〃	
324	〃	CO- 	〃	〃	〃	〃	〃	
325	〃	H	〃	〃	〃	〃	〃	
326	〃	CH_3	〃	〃	〃	〃	〃	

Table 22

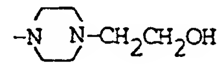
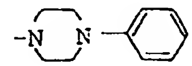
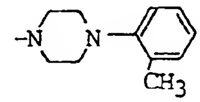
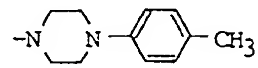
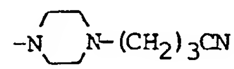
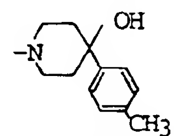
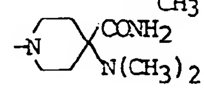
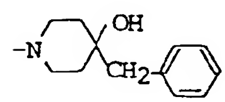
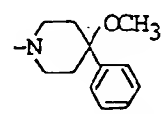
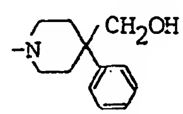
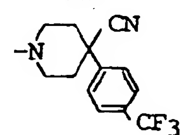
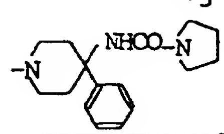
No.	R^1	R^2	A	B	D	n	Q	T
327	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
328	"	"	"	"	"	"	"	
329	"	C_2H_5	"	"	"	"	"	
330	"	Br	"	"	"	"	"	
331	"	"	"	"	"	"	"	
332	"	Cl	"	"	"	"	"	
333	"	"	"	"	"	"	"	
334	"	"	"	"	"	"	"	
335	"	C_2H_5	"	"	"	"	"	
336	"	C_3H_7	"	"	"	"	"	
337	"	CH_3	"	"	"	"	"	
338	"	"	"	"	"	"	"	

Table 23

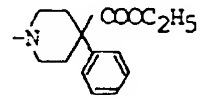
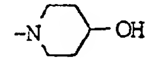
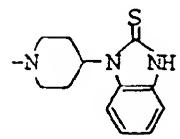
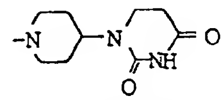
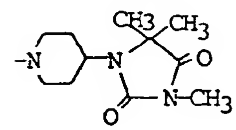
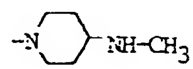
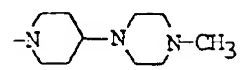
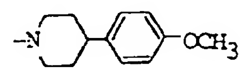
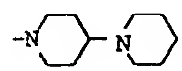
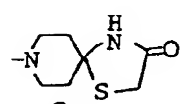
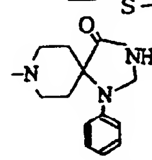
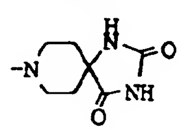
No.	R^1	R^2	A	B	D	n	Q	T
339	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
340	"	"	"	"	"	"	"	
341	"	"	"	"	"	"	"	
342	"	H	"	"	"	"	"	
343	"	"	"	"	"	"	"	
344	"	CH_3	"	"	"	"	"	
345	"	"	"	"	"	"	"	
346	"	"	"	"	"	"	"	
347	"	"	"	"	"	"	"	
348	"	"	"	"	"	"	"	
349	"	"	"	"	"	"	"	
350	"	"	"	"	"	"	"	

Table 24

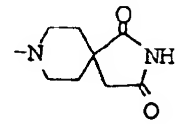
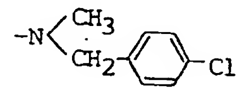
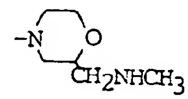
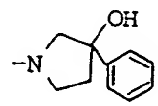
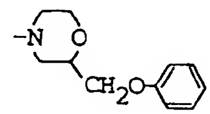
No.	R^1	R^2	A	B	D	n	Q	T
351	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
352	〃	〃	〃	〃	〃	〃	〃	
353	〃	〃	〃	〃	〃	〃	〃	
354	〃	$SO_2N(CH_3)_2$	〃	〃	〃	〃	〃	
355	〃	〃	〃	〃	〃	〃	〃	

Table 25

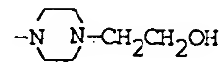
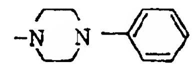
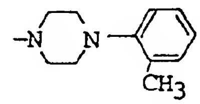
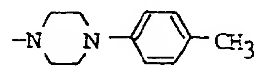
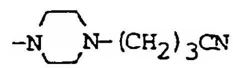
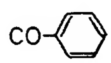
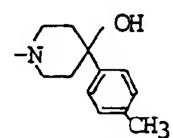
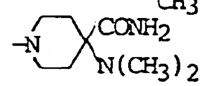
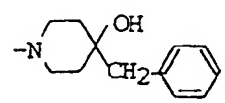
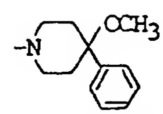
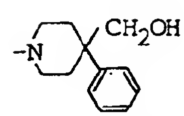
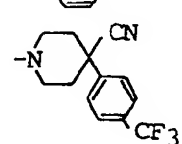
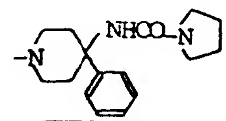
No.	R^1	R^2	A	B	D	n	Q	T
356	H	CH_3	—	C=O	S	2	$-(CH_2)_4-$	
357	〃	〃	〃	〃	〃	〃	〃	
358	〃	〃	〃	〃	SO	〃	〃	
359	〃	〃	〃	〃	S	〃	〃	
360	〃	C_2H_5	〃	〃	〃	〃	〃	
361	〃		〃	〃	〃	〃	〃	
362	〃	〃	〃	〃	〃	〃	〃	
363	〃	COC_2H_5	〃	〃	〃	〃	〃	
364	〃	CH_3	〃	〃	〃	〃	〃	
365	〃	Cl	〃	〃	〃	〃	〃	
366	〃	〃	〃	〃	〃	〃	〃	
367	〃	〃	〃	〃	〃	〃	〃	

Table 26

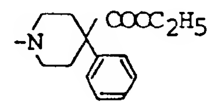
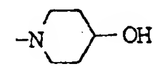
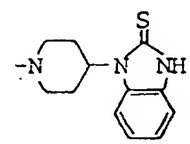
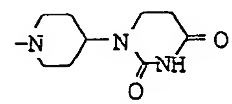
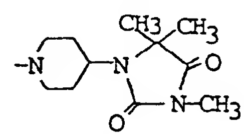
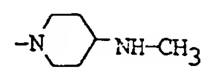
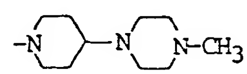
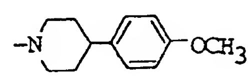
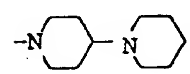
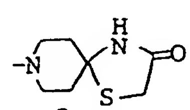
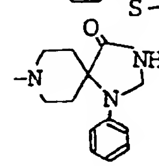
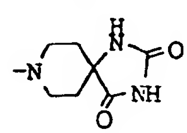
No.	R^1	R^2	A	B	D	n	Q	T
368	H	Br	—	C=O	S	2	$-(CH_2)_4-$	
369	〃	H	〃	〃	〃	〃	〃	
370	〃	CH_3	〃	〃	〃	〃	〃	
371	〃	〃	〃	〃	〃	〃	〃	
372	〃	〃	〃	〃	〃	〃	〃	
373	〃	〃	〃	〃	〃	〃	〃	
374	〃	〃	〃	〃	〃	〃	〃	
375	〃	〃	〃	〃	〃	〃	〃	
376	〃	〃	〃	〃	〃	〃	〃	
377	〃	〃	〃	〃	〃	〃	〃	
378	〃	〃	〃	〃	〃	〃	〃	
379	〃	C_2H_5	〃	〃	SO_2	〃	〃	

Table 27

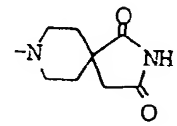
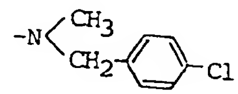
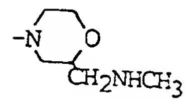
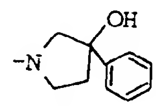
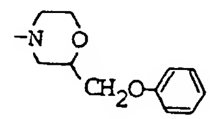
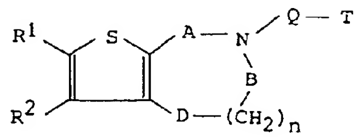
No.	R^1	R^2	A	B	D	n	Q	T
380	H	C_2H_5	—	C=O	SO	2	$-(CH_2)_4-$	
381	〃	〃	〃	〃	〃	〃	〃	
382	〃	H	〃	〃	S	〃	〃	
383	〃	〃	〃	〃	〃	〃	〃	
384	〃	〃	〃	〃	〃	〃	〃	

Table 28



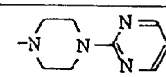
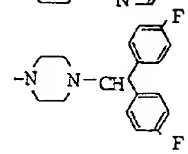
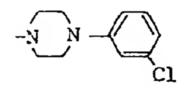
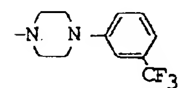
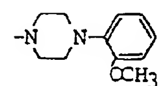
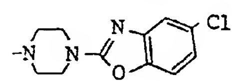
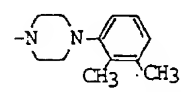
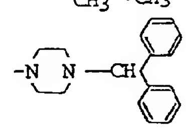
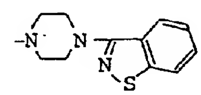
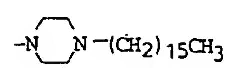
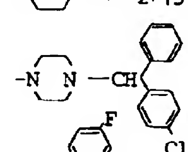
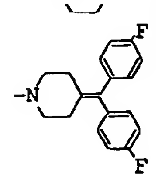
No.	R¹	R²	A	B	D	n	Q	T
385	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
386	″	″	″	″	″	″	″	
387	″	Br	″	″	″	″	″	
388	″	″	″	″	″	″	″	
389	″	Cl	″	″	″	″	″	
390	″	CH_3	″	″	″	″	″	
391	″	SO_2CH_3	″	″	″	″	″	
392	″	$COCH_3$	″	″	″	″	″	
393	″	″	″	″	″	″	″	
394	″	Br	″	″	″	″	″	
395	″	CH_3	″	″	″	″	″	
396	″	″	″	″	″	″	″	

Table 29

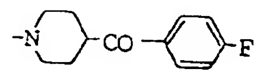
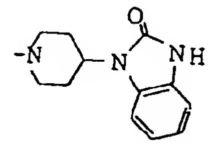
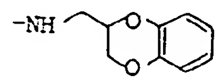
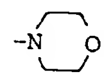
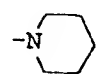
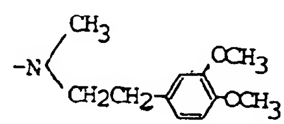
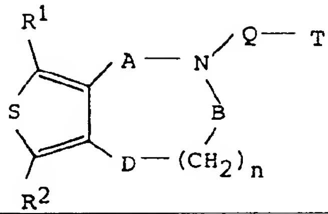
No.	R^1	R^2	A	B	D	n	Q	T
397	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
398	〃	〃	〃	〃	〃	〃	〃	
399	〃	Br	〃	〃	〃	〃	〃	
400	〃	C_2H_5	〃	〃	〃	〃	〃	
401	〃	〃	〃	〃	〃	〃	〃	
402	〃	CH_3	〃	〃	〃	〃	〃	

Table 30



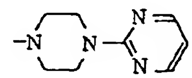
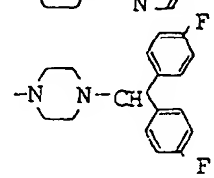
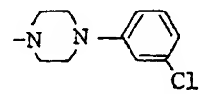
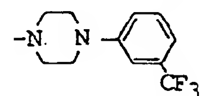
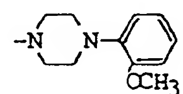
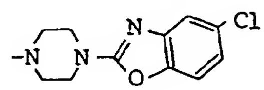
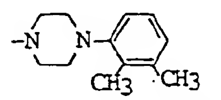
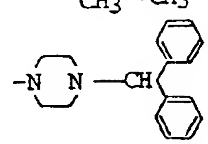
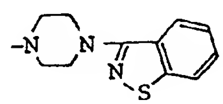
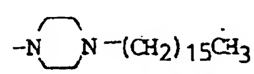
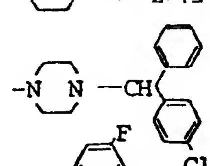
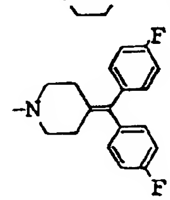
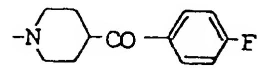
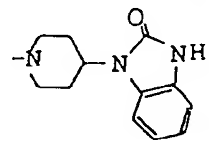
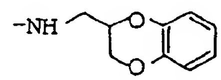
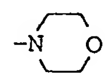
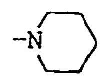
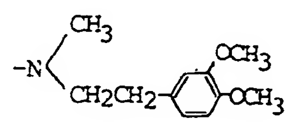
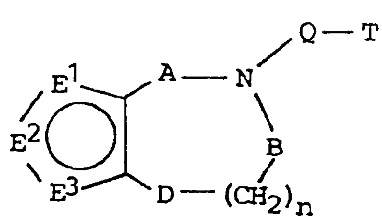
No.	R^1	R^2	A	B	D	n	Q	T
403	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
404	〃	〃	〃	〃	〃	〃	〃	
405	〃	Br	〃	〃	〃	〃	〃	
406	〃	〃	〃	〃	〃	〃	〃	
407	〃	Cl	〃	〃	〃	〃	〃	
408	〃	CH_3	〃	〃	〃	〃	〃	
409	〃	SO_2 CH_3	〃	〃	〃	〃	〃	
410	〃	$COCH_3$	〃	〃	〃	〃	〃	
411	〃	〃	〃	〃	〃	〃	〃	
412	〃	Br	〃	〃	〃	〃	〃	
413	〃	CH_3	〃	〃	〃	〃	〃	
414	〃	〃	〃	〃	〃	〃	〃	

Table 31

No.	R^1	R^2	A	B	D	n	Q	T
415	H	CH_3	C=O	–	CH_2	2	$-(CH_2)_4-$	
416	〃	〃	〃	〃	〃	〃	〃	
417	〃	Br	〃	〃	〃	〃	〃	
418	〃	C_2H_5	〃	〃	〃	〃	〃	
419	〃	〃	〃	〃	〃	〃	〃	
420	〃	CH_3	〃	〃	〃	〃	〃	

Claims

1. A fused thiophene compound of the formula:

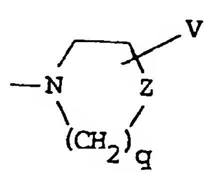
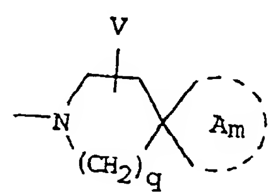


(I)

or a pharmaceutically acceptable acid addition salt thereof, wherein in the above formula, one of E^1, E^2 and E^3 is sulfur atom and other two of them are C-R^1 and C-R^2 respectively; R^1 and R^2 are the same or

different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, arylalkyl, acyl, alkoxyalkyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, hydroxyalkanoyl, aryloxyalkanoyl, haloalkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, arylthio, arylsulfinyl, arylsulfonyl, hydroxysulfonyl, halosulfonyl, sulfamoyl, substituted sulfamoyl, carboxyl, acylamino, alkoxycarbonyl, carbamoyl, substituted carbamoyl or substituted amino; D is $-CH_2-$ or $-S(O)_m-$ (m is 0, 1 or 2; Q is straight or branched chain alkylene. T is primary amino, secondary amino or tertiary amino: A and B are the same or different and each is carbonyl or thiocarbonyl, or one of A and B is absent and the other of them is carbonyl or thiocarbonyl, or A is $-CH_2-$ and B is carbonyl or thiocarbonyl, and n is 1, 2 or 3 with the proviso that n is 2 or 3 when one of A and B is absent and the other of them is carbonyl or thiocarbonyl, and n is 1 or 2 when A and B are other combinations; and wherein the foregoing (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents.

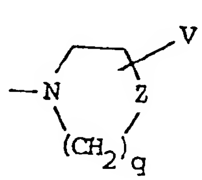
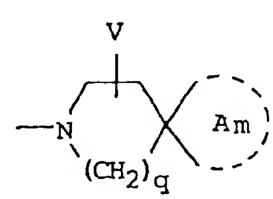
2. The compound or pharmaceutically acceptable acid addition salt thereof of claim 1 wherein T is primary amino of $-NH_2$, T is secondary amino of -NHRa wherein Ra is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl, or T is tertiary amino of -N(Rb)(Rc) wherein Rb and Rc are the same or different and each is alkyl, cycloalkyl, arylalkyl or heteroarylalkyl, or Rb and Rc together with the adjacent nitrogen atom form a cyclic amino of the formula:

(1)  or (2) 

wherein q is an integer of 1 to 4, Z is methylene, oxygen atom, sulfur atom or N-R5 (R5 is hydrogen, alkyl, cyanoalkyl, hydroxyalkyl, aryl, arylalkyl, alkoxycarbonyl, diarylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, acyl, cinnamyl or adamantanemethyl), substituent V is hydrogen, hydroxyl, amino, carbamoyl, mono or di-substituted amino, cyclic amino, acyl, aryl, arylalkyl, arylalkylamino, alkyl, alkoxy, hydroxyalkyl, alkoxycarbonyl, heteroaryl, phenoxyalkyl, anilinoalkyl, alkylaminoalkyl, alkanoylaminoalkyl or bisarylmethylene and the number of V is 1 to 4, and the cyclic amino of formula (1) may contain carbonyl group in the ring and further may be fused with aryl or hetereoaryl; the ring Am of formula (2) may contain amido bond and further may contain oxygen atom, sulfur atom, carbonyl and/or $N-R^6$ (R^6 is hydrogen, alkyl or phenyl), and also the ring Am may be fused with a 5 to 7 membered saturated or unsatured ring, and wherein the (hetero)aromatic ring and the heterocyclic ring may optionally be substituted by 1 to 3 substituents.

3. The compound or pharmaceutically acceptable acid addition salt thereof of claim 1 or 2 wherein T is -NHRa where Ra is heteroarylalkyl which may be optionally substituted by 1 to 3 substituents.

4. The compound or pharmaceutically acceptable acid addition salt thereof of claim 1 or 2 wherein T is -N(Rb)(Rc) where Rb and Rc are the same or different and each is alkyl, arylalkyl or heteroarylalkyl, or Rb and Rc together with the adjacent nitrogen atom form a cyclic amino of the formula:

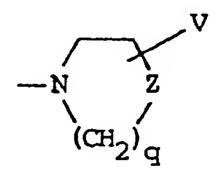
(1)  or (2) 

or

wherein q is an integer of 1 to 4, Z is methylene or $N-R^5$ (R^5 is aryl, diarylalkyl, heteroaryl, heteroarylalkyl

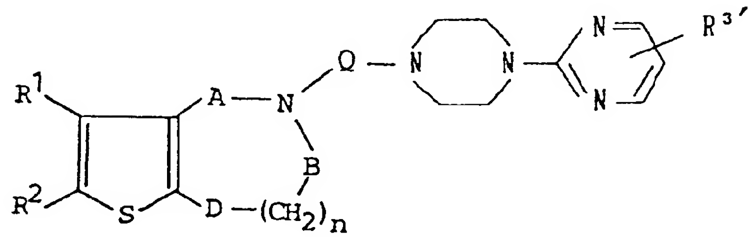
or acyl), substituent V is hydrogen, hydroxyl, carbamoyl, cyclic amino, aryl, arylalkylamino, heteroaryl or bisarylmethylene and the number of V is 1 to 4, wherein the cyclic amino of formula (1) may contain carbonyl group in the ring and further may be fused with aryl or heteroaryl; the ring Am of formula (2) may contain an amido bond in the cycle and further may contain a sulfur atom, and/or N-R^6 (R^6 is phenyl), and further the ring Am may be fused to a 5 to 7 membered saturated or unsatured ring, and in the foregoing (hetero)aromatic ring and the heterocyclic ring may optionally be substituted by 1 to 3 substituents.

5. The compound or pharmaceutically acceptable acid addition salt thereof of claim 1 or 2 wherein T is a cyclic amino of the formula:



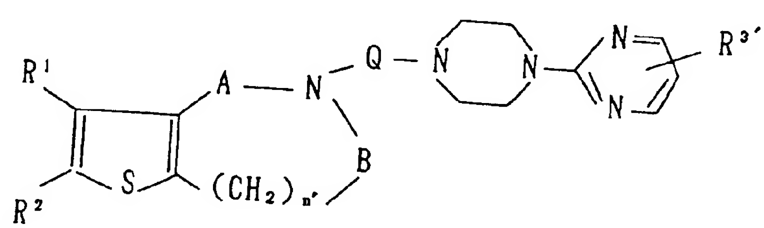
where Z is N-R^5 (R^5 is pyrimidinyl or substituted pyrimidinyl), substituent V is hydrogen, and q is 2.

6. The compound of claim 1 or 2 of the formula:



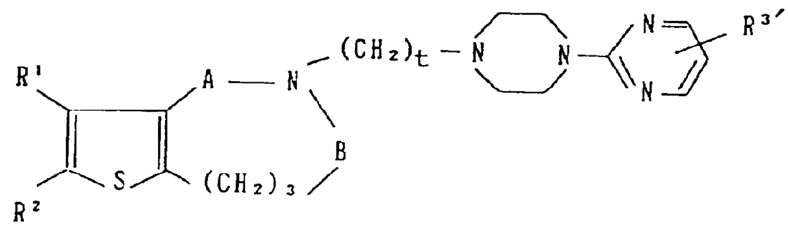
or pharmaceutically acceptable acid addition salt thereof, wherein $R^{3'}$ is hydrogen, halogen, nitro, amino, cyano, hydroxyl, alkyl, alkoxy or haloalkyl and the other symbols are as defined in claim 1 or 2.

7. The compound of claim 1 or 2 of the formula:



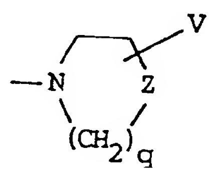
or pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 are the same or different and each is hydrogen, halogen, nitro, amino, cyano, hydroxyl, formyl, alkyl, alkoxy, haloalkyl, aralkyl, acyl, alkoxyalkyl, acyloxyalkyl, hydroxyalkyl, acyloxyalkanoyl, alkoxyalkanoyl, hydroxyalkanoyl, aryloxyalkanoyl or haloalkanoyl, $R^{3'}$ is as defined in claim 6, A and B are carbonyl groups, or one of A and B is absent and the other is carbonyl group, n' is 2 or 3 when A and B are carbonyl groups and n' is 3 or 4 in the other case, and Q is straight or branched chain alkylene having 1 to 10 carbon atoms.

8. The compound of claim 1 or 2 of the formula:



or pharmaceutically acceptable acid addition salt thereof, wherein R^1 and R^2 are as defined in claim 7, $R^{3'}$ is as defined in claim 6, t is an integer of 1 to 8, A and B are absent or carbonyl group, and when A is carbonyl group, B is absent.

9. The compound of claim 1 or 2 or pharmaceutically acceptable acid addition salt thereof, wherein T is a group of the formula:



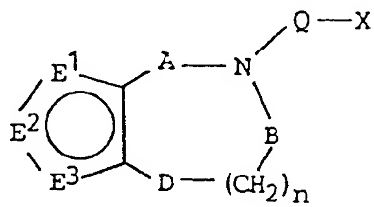
and Z is methylene or N-R^5 (R^5 is aryl, diarylalkyl, heteroaryl except pyrimidinyl, heterarylalkyl or acyl). Substituent V is hydrogen, hydroxyl, carbamoyl, cyclic amino, aryl, arylalkylamino, heteroaryl or bisarylmethylene and the number of V is 1 to 4. q is 2, and wherein the (hetero)aromatic ring and heterocyclic ring may optionally be substituted by 1 to 3 substituents.

10. A compound as claimed in claim 1 which is
2-bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-ethyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-acetyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-(1-hydroxyethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-(4-[(1,4-benzodioxan-2-yl)methylamino]butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno(3,2-f]-1,4-thiazepin-5(4H)-one,
7-bromo-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-ethyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
4-[4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)butyl]-2,3-dihydro-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
4-[4-(4-(bis(4-fluorophenyl)methyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepine-4,6-dione,
7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydro-4H-thieno[3,2-f][1,4]thiazepine-4,5-dione,
5-[4-(4-(3-trifluoromethylphenyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-[4-(4-(2,3-dimethylphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
5-[4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl]-2-methyl-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-methoxyphenyl)-1-piperazinyl)butyl]-7-methyl-thieno[3,2-f]-1,4-thiazepin-5(4H)-one, or
4-[4-(4-(bis(4-fluorophenyl)methylene)piperidino)butyl]-2,3-dihydro-7-methylthieno[3,2-f]-1,4-thiazepin-5(4H)-one or a pharmaceutically acceptable acid addition salt thereof.

11. A compound as claimed in claim 1 which is

2-bromo-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-methyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-ethyl-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-acetyl-5-[4-(4-(2-pyrididinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2-(1-hydroxyethyl)-5-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4-one,
2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-bromo-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-acetyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
7-ethyl-2,3-dihydro-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-thieno[3,2-f]-1,4-thiazepin-5(4H)-one,
2-methyl-5-[4-(4-(2-pyrididinyl)-1-piperazinyl)butyl]-5,6,7,8-tetrahydro-4H-thieno[3,2-c]azepin-4,6-dione or
7-methyl-4-[4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl]-2,3-dihydro-4H-thieno[3,2-f][1,4]thiazepin-3,5-dione,
or a pharmaceutically acceptable acid addition salt thereof.

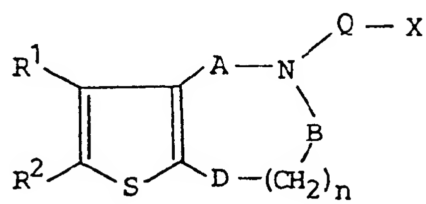
12. A fused thiophene compound of the formula:



(II)

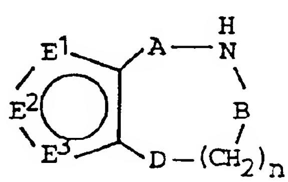
wherein X is hydroxyl, a reactive atom or group derived from hydroxyl, a group of -CO-R^3 (R^3 being hydrogen or alkyl), cyano, carbamoyl or nitro, and other symbols are as defined in claim 1.

13. The compound of claim 12 of the formula:



wherein each symbol is as defined in claims 1 and 12.

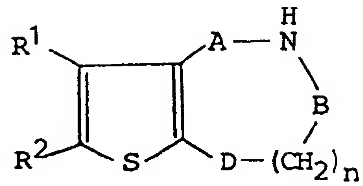
14. A fused thiophene compound of the formula:



(IV)

wherein each symbol is as defined in claim 1.

15. The compound of claim 14 of the formula:



wherein each symbol is as defined in claim 1.

16. A pharmaceutical composition comprising a fused thiophene compound of pharmaceutically acceptable acid addition salt thereof as claimed in any one of claims 1 to 11 and one or more pharmaceutical carrier, diluent or excipient.

17. The use of a compound as claimed in any one of claims 1 to 11 in the preparation of a medicament for treating anxiety, the compound being an antianxietic drug.

18. The use of a compound as claimed in any one of claims 1 to 11 in the preparation of a medicament for treating psychosis, the compound being an an antipsychotic drug.

19. The use of a compound as claimed in any one of claims 1 to 11 in the preparation of a medicament for treating a disease of the circulatory system.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 91306095.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP - A2 - 0 324 610 (LILLY INDUSTRIES LIMITED) * Abstract *	1,6,7, 9,12, 14,16-19	C 07 D 495/04 A 61 K 31/55 A 61 K 31/395
A	EP - A2 - 0 329 168 (BRISTOL-MYERS COMPANY) * Claims 1,7,10 *	1,6,7, 9,12, 14,16-19	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 495/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	16-09-1991	BRUS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) **Combination therapy for peptic ulcer treatment.**

(57) Peptic ulcer disease is treated with a combination therapy of famotidine or omeprazole plus a bismuth salt.

EP 0 480 691 A2

BACKGROUND OF THE INVENTION

In the past, treatment of peptic ulcer disease was based on either neutralization of intragastric acidity with antacids or the inhibition of production of acid secretion by H_2-receptor antagonists or by proton pump inhibition among others. Using bismuth salts alone to heal ulcers has been shown to be effective presumably because of its effect on Helicobacter pylori. Relapse of Helicobacter positivity, however, has been a problem as has relapse of ulcer disease in patients treated with antisecretory therapy.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide compositions and methods of treatment of ulcer disease. Another object is to provide compositions that increase the rate of healing of ulcer disease. A further object is to reduce the relapse and recurrence rate of ulcer disease. Still another object is to provide methods of treating ulcer disease. These and other objects of the present invention will be apparent from the following description.

SUMMARY OF THE INVENTION

Peptic ulcer disease is treated with a combination therapy of famotidine or omeprazole plus a bismuth salt including bismuth carbonate, bismuth subcarbonate, bismuth subcitrate, bismuth subgallate, bismuth subnitrate and bismuth subsalicylate.

DETAILED DESCRIPTION

The present invention relates to peptic ulcer disease, and most particularly to duodenal ulcer disease and gastric ulcer disease.

Suspensions of bismuth salts have long been used for gastro-intestinal upsets. While these salts have little or no acid-neutralizing activity, they inhibit pepsin, increase mucus secretion and interact with proteins in the necrotic ulcer crater where they presumably form a barrier to acid diffusion.

Famotidine, an H_2 antagonist, inhibits gastric acid secretion elicited by histamine and other H_2 agonists and also inhibits acid secretion elicited by gastrin and, to a lesser extent, by muscarinic agonists. The clinical use of famotidine stems largely from its capacity to inhibit gastric acid secretion, especially in patients with peptic ulceration. It is useful to treat duodenal ulcer, gastric ulcer, gastroesophageal reflux disease and maintenance for these conditions and for Zollinger-Ellison syndrome.

Omeprazole, an inhibitor of H^+,K^+-ATPase, offers a means to inhibit profoundly acid secretion to any desired level. It is especially useful in patients with gastroesophageal reflux disease and in patients whose peptic ulcer disease is not well controlled by H_2 antagonists.

It has now been found that combinations of famotidine or omeprazole with a bismuth salt offer greater initial healing of ulcer disease, or more rapid healing of ulcer disease, or greater initial healing of ulcer disease combined with more rapid healing. These combinations also decrease the frequency of recurrence of ulcer disease over time.

Famotidine is disclosed in U.S. patent 4,283,408. Its efficacy in inhibiting gastric acid and pepsin secretion in man is described by Miwa et al., J. Clin. Pharmacol. Ther. Toxicol. 22, 214 (1984). The results of a clinical trial in Zollinger-Ellison syndrome are described by Howard et al., Gastronenlerology 88, 1026 (1985). Symposia on the pharmacology and clinical efficacy of famotidine are reported in Am. J. Med. 81, Suppl. 4B, 1-64 (1986), and in Scand. J. Gastroenterol. 22, suppl. 134, 1-62 (1987).

Omeprazole is disclosed in U.S. patent 4,255,431. Its pharmacology is described by Muller et al., Arzneimittel-Forsch. 33, 1685 (1983). The results of a clinical trial in Zollinger-Ellison syndrome are described by Lamers et al., N. Engl. J. Med. 310, 758 (1984), and in duodenal ulcer by Lauritsen et al., ibid. 312, 958 (1985), and by Pritchard et al., Brit. Med. J. 290, 601 (1985). A review of pharmacodynamics, pharmacokinetics and therapeutic use is given by Clissold et al., Drugs 32, 15-47 (1986).

The bismuth salts employed in the combinations of the present invention include any bismuth salt useful in treating gastro-intestinal upsets. Examples of such salts are bismuth carbonate, bismuth subcarbonate, bismuth subcitrate, bismuth subgallate, bismuth subnitrate and bismuth subsalicylate.

The combination therapy of the present invention comprises famotidine in a dosage range of from about 10 to about 80 mg/day, typically about 40 mg h.s. or omeprazole in the range of from about 10 to about 80 mg/day, typically about 20 mg a.m., with a bismuth salt useful in treating gastrointestinal upsets in a dosage range of from about 400 to about 600 mg/day in divided doses.

Specific examples of the combination therapy of the present invention follow. The indicated quantity of

famotidine or omeprazole is combined with the indicated quantity of any one of the bismuth salts in the same column.

	mg/day							
Famotidine	10	20	30	40	50	60	70	80
Bismuth carbonate	400	450	500	550	600	400	450	500
Bismuth subcarbonate	550	600	400	450	500	550	600	400
Bismuth subcitrate	450	500	550	600	400	450	500	550
Bismuth subgallate	600	400	450	500	550	600	400	450
Bismuth subnitrate	500	550	600	400	450	500	550	600
Bismuth subsalicylate	400	450	500	550	600	400	450	500

Omeprazole	10	20	30	40	50	60	70	80
Bismuth carbonate	550	600	400	450	500	550	600	400
Bismuth subcarbonate	450	500	550	600	400	450	500	550
Bismuth subcitrate	600	400	450	500	550	600	400	450
Bismuth subgallate	500	550	600	400	450	500	550	600
Bismuth subnitrate	400	450	500	550	600	400	450	500
Bismuth subsalicylate	550	600	400	450	500	550	600	400

Claims

1. A composition for treating peptic ulcer disease comprising a combination of from about 10 to about 80 mg/day of a gastric acid inhibitor selected from famotidine and omeprazole with from about 400 to about 600 mg/day of a bismuth salt useful in treating gastrointestinal upsets.

2. A composition according to claim 1 wherein the gastric acid inhibitor is famotidine.

3. A composition according to claim 1 wherein the gastric acid inhibitor is omeprazole.

4. A composition according to claim 1 wherein the bismuth salt is bismuth carbonate, bismuth subcarbonate, bismuth subcitrate, bismuth subgallate, bismuth subnitrate or bismuth subsalicylate.

5. The use of a composition according to claim 1 for the manufacture of a medicament for treating peptic ulcer disease.

6. A product containing from about 10 to about 80 mg/day of a gastric acid inhibitor selected from famotidine and omeprazole, and from about 400 to about 600 mg/day of a bismuth salt useful in treating gastrointestinal upsets, for simultaneous, separate or sequential use in the treatment of peptic ulcer disease.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

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(54) **Use of specific core material and layers to obtain pharmaceutical formulations stable to discolouration of omeprazole.**

(57) The use of core material in the form of small beads or tablets containing as the active compound omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating, in order to obtain an oral pharmaceutical preparation of omeprazole which is stable to discolouration.

EP 0 496 437 A2

The present invention is related to a new stable pharmaceutical preparation containing omeprazole for oral use, and to a method for the manufacture of such a preparation.

From e.g. EP-A1-0 005 129 omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole, a potent inhibitor of gastric acid secretion is known. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov 27, 1982, p. 1223-1224) and can be used for the treatment of gastric and duodenal ulcers. Omeprazole is, however, susceptible to degradation/transformation in acid reacting and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH = 7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture and organic solvents.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

In human pharmacological studies it was found that the rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole to the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal.

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become rapidly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phtalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alakaline solution will interfere with the enteric coating and eventually dissolve it.

An enteric coated dosage form of omeprazole was reported by Pilbrant and Cederberg, in the above cited Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120. The publication describes a conventional enteric coated dosage form and states that it has an acceptable storage stability - for clinical studies. It was later found that the stability of this dosage form was insufficient during long-term storage required for a marketed pharmaceutical dosage form.

If a conventional formulation of omeprazole is made, the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

In DE-A1-3046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of omeprazole in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing omeprazole since direct contact between substances such as cellulose acetate phthalate (CAP) and omeprazole causes degradation and discolouration of omeprazole.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of omeprazole in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastrice but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric

coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for omeprazole, where a rapid release of the drug in the small intestine is needed.

DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention.

GB-A-1 485 676 describes a way to obtain a preparation, which effervesces in the small intestine, by enteric coating a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. The formulation cannot be adopted for a pharmaceutical dosage form containing omeprazole, as the presence of an acid in contact with omeprazole in the cores would give a result that omeprazole was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for omeprazole where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing omeprazole.

EP-A-124 495 describes enteric coated granules without subcoating or powder that are filled into hard gelatine capsules or a solution that is filled into soft capsules.

The object of the present invention is to provide an enteric coated dosage form of omeprazole, which is stable to discolouration and which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability during long-term storage. The new dosage form is characterized in the following way. Core material in the form of small beads or tablets containing omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating. This/these inner layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability of the dosage form during long-term storage.

Detailed description of the invention

Cores

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less that pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $A1_2O_3.6MgO.CO_2.12H_2O$,$(Mg_6A1_2(OH)_{16}CO_3.4H_2O)$, $MgO.A1_2O_3.\ 2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of omeprazole such as the sodium, potassium, magnesium, calcium etc. salts of omeprazole, which are described in e.g. EP-A2-124 495, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer-(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the

separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_36MgO.CO_212H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_32SiO_2.nH_2O$ or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or polyvinyl acetal diethylaminoacetate. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

Enteric coating layer

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions on said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing omeprazole mixed with an alkaline reacting compound or cores containing an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound. The alkaline reacting core material and/or alkaline salt of the active ingredient, omeprazole, enhance the stability of omeprazole. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with an inert reacting water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores form the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and/or the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing omeprazole (enteric coated tablets, capsules or pellets) is kept low, preferably not more than 1.5 % by weight. As a consequence the final package containing hard gelatin capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the gelatin shell to a level where the water content of the enteric coated pellets filled in the capsules does not exceed 1.5 % by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

The effect of different magnesium compounds was evaluated in the form of enteric coated tablets. Tablet cores were first made by known techniques according to the formulations listed in Table 1, followed by application of separating layers and enteric coating layers shown in Table 2.

Table 1

Formulations for the tablet cores (mg)							
Formulations No.	1	2	3	4	5	6	7
Omeprazol	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Lactose	134.0	119.0	119.0	119.0	118.8	118.5	119.0
Hydroxypropyl cellulose (low substitution	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropyl cellulose	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Na_2HPO_4	-	15.0	-	-	0.2	-	-
Na lauryl sulfate	-	-	-	-	-	0.5	-
MgO	-	-	15.0	-	-	-	-
$Mg(OH)_2$	-	-	-	15.0	15.0	15.0	-
Synthetic hydrotalcite [$A1_2O_3.6MgO.CO_2.12H_2O$]	-	-	-	-	-	-	15.0
Total	160.0	160.0	16.0	160.0	160.0	160.0	160.0

Table 2 Formulations for coatings (mg)

Formulation No.	I	II	III	IV
Separating layer (inner):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Magnesium hydroxide	-	-	0.3	-
Synthetic hydrotalcite	-	-	-	0.3
Separating layer (outer):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Enteric coating layer:				
Hydroxypropyl methylcellulose phthalate	7.0	7.0	7.0	7.0
Cetyl alcohol	0.5	0.5	0.5	0.5

The tablets thus otained were stored in open form under so called accelerated conditions, that is 40 ° C, and 75 % relative humidity, and the changes in appearance with the passage of time were observed. Storage for six months under these conditions corresponds to storage at normal temperature for three years. This means that high stability sufficient for practical use may be assured if a drug remains intact for about one week under the mentioned conditions. The result is summarized in Table 3. As may be seen from the table, a remarkable stabilizing effect is achieved when a magnesium compound is contained in the inner layer.

Table 3

Stabilizing Effect (Appearance of Preparations)								
Coating Layer		Core material						
		1	2	3	4	5	6	7
I	At the start	C	A	A	A	A	A	A
	60 ° C; after 7 days	E	D	C	C	C	C	D
	40 ° C; 75% RH; after 7 days	F	E	B	B	B	B	E
II	At the start	A	A	A	A	A	A	A
	60 ° C; after 7 days	E	B	A	A	A	A	C
	40 ° C; 75% RH; after 7 days	E	D	A	A	A	A	D
III	At the start	A	A	A	A	A	A	A
	60 ° C; after 15 days	B	A	A	A	A	A	A
	40 ° C; after 30 days	A	A	A	A	A	A	A
	40 ° C; 75% after 15 days	B	A	A	A	A	A	A
IV	At the start	A	A	A	A	A	A	A
	60 ° C; after 15 days	B	A	A	A	A	A	A
	40 ° C; after 30 days	A	A	A	A	A	A	A
	40 ° C; 75% RH; after 15 days	B	A	A	A	A	A	A
A: white, B: brownish white, C: faint brown, D: light brown, E: brown, F: deep brown.								

All the samples evaluated as A (white) in the above table showed no discoloration even on split surfaces. The samples evaluated as B (brownish white) showed little change in appearance, but some discoloration was observed on split surfaces.

Table 4 shows the result of a stability test on the omeprazole preparation according to Example 1 (Formulation No 4-IV). The formulation was stored in a closed glass bottle at room temperature for the indicated period of time. This clearly demonstrates that preparations with unusually high stability were obtained.

Table 4

Stability of enteric coated omeprazole preparations (Tablets of Formulation No.4-IV)		
Storage Period	Appearance	Omeprazole Content(%)
At the start of test	White	100.0
1 year at room temp.	White	99.9
2 years at room temp.	White	100.0

Example 2

Uncoated pellets

I	Mannitol powder	16 150	g
	Lactose anhydrous	800	g
	Hydroxypropyl cellulose	600	g
	Microcrystalline cellulose	400	g
II	Omeprazole	2 000	g
	Sodium lauryl sulphate	50	g
	Disodium hydrogen phosphate	80	g
	Distilled water	4 400	g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated omeprazole pellets	6 000	g
III	Hydroxypropyl methylcellulose	240	g
	Distilled water	4 800	g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric-coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 225 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

Example 3

This example illustrates that a variety of polymers can be used for subcoating, e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols.

Uncoated pellets

I	Mannitol powder	1 620 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Sodium lauryl sulphate	1.0 g
	Disodium hydrogen phosphate	9.3 g
	Distilled water	515 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

III	Uncoated omeprazole pellets	500 g
	Polyvinylpyrrolidone	20 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric-coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methyl-cellulose phthalate	45 g
	Cetyl alcohol	5 g
	Acetone	219 g
	Ethanol	680 g

The enteric-coated pellets were prepared as described in Example 2.

Example 4

Uncoated pellets

I	Mannitol powder	1 610	g
	Lactose anhydrous	80	g
	Hydroxypropyl cellulose	60	g
	Microcrystalline cellulose	40	g
II	Omeprazole	200	g
	Pluronic® F68	10	g
	Disodium hydrogen phosphate	24	g
	Distilled water	450	g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

	Uncoated pellets	500	g
III	Polyvinylpyrrolidone	30	g
	Ethanol	400	g

The subcoated pellets were prepared as described in Example 2.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methyl-cellulose phthalate	45	g
	Cetyl alcohol	5	g
	Methylene chloride	371	g
	Ethanol	680	g

The enteric coated pellets were prepared as described in Example 2.

Example 5

This example illustrates that a variety of polymers can be used as enteric coating material e.g. cellulose acetate phthalate, poly-(vinyl acetate/vinyl alcohol phthalate), hydroxypropyl methyl cellulose phthalate, poly-(methacrylic acid/methacrylic acid methyl esters), poly-(acrylic acid/methacrylic acid methyl esters). The polymers can be applied with/without plasticizer, e.g. polyethylene glycols, triacetin, dimethyl polysiloxan, Citroflex®, cetyl alcohol, stearyl alcohol, diethyl phthalate.

Enteric-coated pellets can also be manufactured from water-based polymer dispersions, e.g.

Aquateric®(FMC Corporation), Eudragit®L 100-55, Coating CE 5142 (BASF).

Uncoated pellets

I	Lactose powder	277 g
	Lactose anhydrous	118 g
	Hydroxypropyl cellulose	25 g
	Colloidal silica	25 g
II	Omeprazole	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	2 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	170 g

The uncoated pellets were prepared as described above.

Subcoated pellets

The uncoated pellets were subcoated as described in Example 2.

Enteric coated pellets

	Subcoated pellets	500 g
III	Eudragit®L 500	45 g
	Stearyl alcohol	4.5 g
	Ethanol	1 320 g

The enteric coated pellets were prepared as described above.

Example 6

Formulations with the sodium salt of omeprazole.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 2 with the exception that the omeprazole sodium salt was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g

IV	Pellets subcoated with III	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500 g
V	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 2.

Examples 7 and 8

Formulations with the magnesium salt of omeprazole.

Uncoated pellets		Example No 7	Example No 8
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1 673 g	1 473 g
	Microcrystalline cellulose	100 g	100 g
	Magnesium hydroxide	-	200 g
II	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole salt was added together with the other ingredients in mixture I.

Subcoated pellets		Examples 7 and 8
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

Enteric coated pellets		Examples 7 and 8
	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

Examples 9 and 10

Manufacture of tablets.

Tablet cores		Examples No 9	10
I	Omeprazole	400 g	-
	Omeprazole sodium salt, corresponding to omeprazole 400 g	-	426 g
	Lactose, anhydrous	1 420 g	1 406 g
	Polyvinylpyrrolidone, crosslinked	100 g	100 g
	Sodium carbonate, anhydrous	15 g	-
II	Methyl cellulose	12 g	12 g
	Distilled water	200 g	200 g
III	Magnesium stearate	30 g	30 g

The powder mixture I was carefully homogenized and granulated by the solution II. The wet mass was dried in a fluidized bed dryer using an inlet air temperature of +50°C for 30 minutes. The dried mixture was then forced through a sieve with an apperture of 0.5 mm. After mixing with magnesium stearate the granulate was tabletted on a tabletting machine using 6 mm punches. The tablet weight was 100 mg.

Subcoating

The tablets containing omeprazole were subcoated with approximately 10 % by weight of hydroxypropyl methylcellulose from a water solution using a perforated coating pan apparatus.

The tablets containing omeprazole sodium salt were subcoated using the dry coating technique. A tablet granulate containing

Lactose anhydrous	4 000 g
Polyvinylpyrrolidone, (PVP)	180 g
Ethanol 95 %	420 g
Magnesium stearate	42 g

was prepared in the following way. The lactose was granulated with a solution of PVP in ethanol and dried. After drying magnesium stearate was admixed.

The granulate mass was dry coated around the tablet cores of Example 9 using a Manesty Dry Cota® tabletting machine. The tablet weight of the dry coated tablets was 475 mg. Each tablet contained 20 mg of omeprazole.

Enteric coating

The subcoated tablets obtained above were enteric coated using the same coating solution:

Hydroxoypropyl methylcellulose phthalate	1 500 g
Cetyl alcohol	105 g
Methylene chloride	15 000 g
Isopropanol	15 000 g
Distilled water	3 150 g

The coating was applied in a perforated coating pan apparatus. An approximate amount of one kg of coating solution was applied for each kg of tablets.

COMPARATIVE EXAMPLES

Examples I, II and III

These examples illustrate that the buffer salt used effects the enteric-coated omeprazole pellets properties when the sub-coating layer is absent. A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellets shows inferior acid resistance properties. C.f. also the Example 4 above.

Uncoated pellets

		Examples No I	II	III
I	Mannitol powder	1 610 g	1 610 g	1 610 g
	Lactose anhydrous	80 g	80 g	80 g
	Hydroxypropyl cellulose	60 g	60 g	60 g
	Microcrystalline cellulose	40 g	40 g	40 g
II	Omeprazole	200 g	200 g	200 g
	Pluronic®F68	10 g	10 g	10 g
	Disodium hydrogen phosphate	2 g	8 g	24 g
	Distilled water	450 g	450 g	450 g

The uncoated pellets were prepared as described in Example 2 above.

Enteric coated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The coated pellets were prepared as describee in Example 2 above.

Example IV

This formulation is the same as in Example 6 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 6.

Enteric-coated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The enteric coated pellets were prepared as described in Example 2.

Example V

This formulation is the same as in Example 8 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole magnesium salt	222	g
	Mannitol powder	1 473	g
	Microcrystalline cellulose	100	g
	Magnesium hydroxide	200	g
II	Sodium lauryl sulphate	5	g
	Distilled water	375	g

The preparation was made as described in Example 8.

Enteric coated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The pellets were prepared as described in Example 2 above.

Properties of the enteric coated pellets

For the preparations according to Examples 2-8 and comparative Examples I-V above one or both of the following studies have been performed.

Acid resistance

The following resistance of the formulations was studied in the following way: The formulations were added to gastric fluid USP (without enzyme), 37° C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulations was determined.

Rate of dissolution in buffer solution

In order to establish the rate of dissolution in the small intestine the formulations were added to a buffer solution. Buffer solution 37° C, USP dissolution apparatus No 2 (paddle), 100 r/min. After 10 or 30 minutes the amount of omeprazole dissolved was determined. The results are presented in the following Table 5.

Table 5

Example No	Omeprazole content mg/g	Acid resistance amount intact omeprazole (%) after 2 hours	% dissolved omeprazole at different pH:s and after 10 or 30 min		
			%	pH	min
2	89.2	96	100	6.8	10
3	90	96	91	6.0	10
4	88	89	*)		
5	82	93	70	7.5	30
6	81.3	87	93	6.8	10
7	91	95	**)		
8	89	98	**)		
I	93	97	*)		
II	92	94	*)		
III	94	58	*)		
IV	86.5	4			
V	91	93	**)		

*) The stability of the formulation was studied during storage in glass bottles also containing a desiccant device. After one month storage at +50 °C the formulation according to Example 4 was virtually intact with no change in appearance or physicochemical characteristics. Pellets according to Example I and II turned brown due to degradation, while the pellets according to Example III retained to original white colour.

**) The formulations according to Examples 7 and 8 were white and not affected by the coating process. The enteric coated pellets according to Example V, where the enteric coating was applied directly on the cores according to Example 8, was discoloured already during the enteric coating process.

Further comparative test

This example demonstrates the effect of the moisture content of the preparations according to the invention on storage stability.

The stability of omeprazole pellets according to the invention was compared with that of omeprazole pellets with higher water content. Omeprazole pellets were prepared according to the invention with a water content of 1 %. Two other portions of the same formulation were conditioned to a water content of 2 % and 5 % respectively. The three formulations, packed in tight containers not containing a desiccant, were stored for one month at + 50 °C. After this time the packages were opened and the pellets were assayed for the amount of omeprazole by HPLC. The formulation according to the invention had an omeprazole content of 98.5 % of the initial value. The other two formulations with at water content of 2 and 5 % respectively were totally degraded and had only trace amounts of intact omeprazole.

DISCUSSION

From the results given in Table 5 it can be seen that formulations containing omeprazole with acceptable acid resistance can be prepared by using a conventional enteric coating technique (see for instance Examples I, II and V). However, it is also obvious that the storage stability of the formulations according to Examples I, II and V is not acceptable, since a discolouration, showing a degradation of omeprazole, occurs during short storage at an elevated storage temperature (Examples I and II) or already during the enteric coating process (Example V).

If the amount of alkaline substances in the cores is increased to a level where omeprazole has an acceptable storage stability (Example III) or if an alkaline reacting salt of omeprazole is used in the preparation of the cores (Example IV), then, without the separating layer of the invention, the resistance to dissolution in acid media becomes unacceptably low and much or all of the active substance will degrade already in the stomach and thus, it has no effect on the gastric acid secretion.

When the preparation is carried out to the invention as for instance in Example 4, a good resistance towards gastric juice as well as a good stability during long-term storage is obtained. This is in contrast with

the formulations in Examples I, II and III where either an acceptable acid resistance or an acceptable storage stability can be achieved - but not both. The same comparison can be made between the formulations according to Examples 7 and 8 according to the invention and the formulation according to Example V, where the separating layer was omitted. Examples 7 and 8 differ in that a buffering substance, magnesium hydroxide, has been included in the cores of Example 8. This further improves the acid resistance as well as the storage stability of Example 8 in comparison with Example 7.

The further comparative test shows the great importance of a low water content in the preparations.

Thus, in order to prepare pharmaceutical formulations of omeprazole for oral use, which exert good stability during long-term storage as well as good stability during the residence in the stomach after administration, the preparation is made in the following way:

a) Omeprazole together with an alkaline reacting compound or compounds or an alkaline reacting salt of omeprazole optionally mixed with alkaline reacting compound are included in the core material.

b) The core material is subcoated with one or more inert, in water soluble or in water rapidly disintegrating layers, which separate the alkaline reacting core from the enteric coating. The subcoating layer may optionally contain pH-buffering compounds.

c) The subcoated cores are coated with an acid insoluble enteric coating, optionally containing plasticizers.

Biopharmaceutical studies

The hard gelatin capsules according to Example 2 were administered to 12 healthy, young male volunteers in the following way:

The volunteers came to the laboratory in the morning after having abstained from food since 10 p.m. the night preceeding the experimental day. A zero time blood sample was taken. One omeprazole capsule according to Example 2 was administered together with 150 ml of tap water. Further blood samples were taken during the day.

In another experiment the same volunteers were administered 20 mg of omeprazole in the form of a suspension of micronized omeprazole in a sodium bicarbonate water solution. In order to reduce the degradation of omeprazole in the stomach to a minimum, solid bicarbonade solution was given to the subjects just before the administration of the omeprazole suspension and at further four times with a 10-minutes interval after the drug intake. The concentration of omeprazole in blood plasma was assayed by high pressure liquid chromatography (Persson, Lagerström and Grundevik. Scand J Gastroenterol 1985, 20, (suppl 108), 71-77. The mean plasma concentrations are given in Table 6.

Table 6

The plasma concentrations (μmol/l) after 20 mg single oral doses of omeprazole given as hard gelatin capsules according to Example 2 and as a suspension of micronized omeprazole in sodium bicarbonate solution.

Time (min)	Capsules	Suspension
10		0.84
20		0.90
30	0.03	0.84
45		0.64
60	0.22	0.44
90	0.36	0.24
120	0.39	0.13
150	0.29	
180	0.20	0.04
210	0.10	
240	0.05	0.01
300	0.02	0
360	0.01	
420	0	

Although the plasma concentration peak at different times, the two formulations are bioequivalent. The mean relative bioavailability of the capsules in comparison with the suspension was 85 % +23 % (S.D.). The comparison was based on the total area under individual plasma concentration versus times curves.

Thus, by preparing capsules according to the invention it is possible to obtain a preparation with the same bioavailability as a suspension containing the same amount to micronized active compound. It is, however, to be noticed that when the suspension is administered, the patients must also be given sodium bicarbonate solution frequently in order to minimize pre-absorption degradation of omeprazole in the stomach.

Claims

1. The use of core material in the form of small beads or tablets containing as the active compound omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating, in order to obtain an oral pharmaceutical preparation of omeprazole which is stable to discolouration.

2. The use according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

3. The use according to claim 1 wherein the sub-coating comprises two or more sub-layers and where the inner sublayer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, wherein n is not an integer and less than 2.

4. The use according to claim 1 wherein the alkaline core comprises omeprazole and pH-buffering alkaline compound rendering to the micro-environment of omeprazole a pH of 7-12.

5. The use according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$ or $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, where n is not an integer and less than 2.

6. The use according to claim 1 wherein the alkaline core comprises an alkaline salt of omeprazole such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. The use according to claim 6 wherein the alkaline core comprises an alkaline salt of omeprazole mixed with an alkaline compound.

8. The use according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. The use according to claim 1 wherein the water content of the final dosage form containing omeprazole does not exceed 1.5 % by weight.

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(54) Use of specific core material and layers to obtain pharmaceutical formulations stable to discolouration of acid labile compounds.

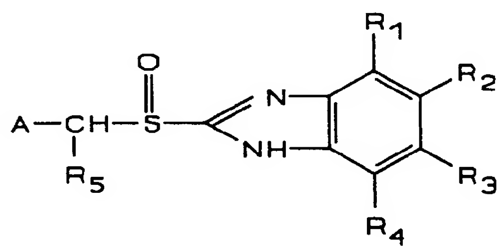
(57) The use of core material in the form of small beads or tablets containing as the active ingredient an acid labile compound of the general formula I and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, in order to obtain an oral preparation stable to discolouration.

EP 0 502 556 A1

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



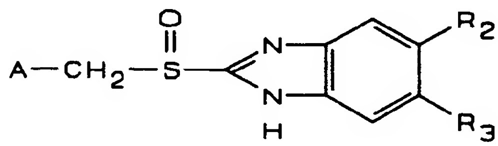
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4, are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

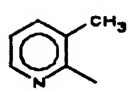
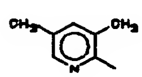
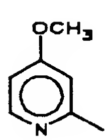
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

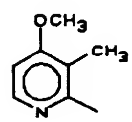
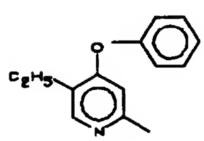
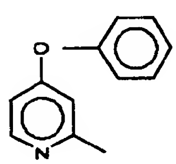
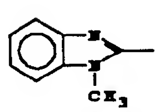
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No A	R^2 R^3	Half-life (minutes for the transformation to the active moiety at pH=2	at pH=7
1.	5-$COOCH_3$;6-CH_3	11	150
			
2.	5-CH_3;H	5.4	1700
			
3.	5-CF_3;H	1.9	122
			

Cont.

Compound No			Half-life (minutes for the transformation to the active moiety	
	A	R^2 R^3	at pH=2	at pH=7
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact

with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3, and R^4, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

$$-O-\overset{\overset{\displaystyle O}{\|}}{C}-\text{lower alkyl}$$

or halogen and R^5 is H or lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acide labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient

together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

R^1, R^2, R^3 and R^4, which are the same or different and especially

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) -CN
(d) -CHO
(e) $-CF_3$
(f)

$$-\overset{\overset{\displaystyle O}{\|}}{C}-R^{11}$$

(g) $-O-C-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(l) -alkylthio containing 1-6 carbon atoms
(m) $-NO_2$
(n) -akylsulfinyl containing 1-6 carbon atoms
(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 subsituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of theses substituents together form one or two oxo groups

$$(-\overset{\overset{\displaystyle O}{\|}}{C}-),$$

whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same of different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxyalkoxy containing 1-4 carbon atoms
(c) alkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is
(a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is -O- or

$$-\overset{\overset{\displaystyle O}{\|}}{C}- \;;$$

n is 0 or 1;

B is
(a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkynylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c)

$$-\overset{O}{C}-R^{9}$$

(d)

$$-(Y)_{m}-(\overset{O}{C})_{r}-R^{10}$$

wherein

R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

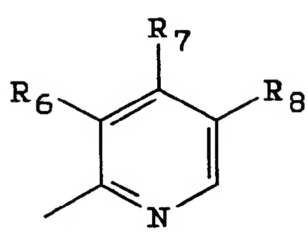
r is 0 or 1;

Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;

R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or
(b) alkyl containing 1-6 carbon atoms;

R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(f) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$
$-O-(CH_2)_p-$
$-S-(CH_2)_v-$
$-CH_2(CH_2)_p-$
$-O-CH=CH-$
$-NH-CH=CH-$

$$-\underset{\substack{|\\ CH_3}}{N}-CH=CH-$$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less that pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $A1_2O_3.6MgO.CO_2.12H_2O$,$(Mg_6A1_2(OH)_{16}CO_3.4H_2O)$, $MgO.A1_2O_3$. $2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $A1_2O_3 \cdot 6MgO \cdot CO_2 12H_2O$, $(Mg_6A1_2(OH)_{16}CO_3 \cdot 4H_2O)$, $MgO \cdot A1_2O_3 \cdot 2SiO_2 \cdot nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC

Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253 g
	Lactose anhydrous	167 g
	Hydroxypropyl cellulose	25 g

II	Compound 1, Table 1	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5g
	Sodium dihydrogen phosphate	0.1g
	Distilled water	125 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methyl-cellulose	20 g
	Distilled water	400 g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table 1.

Uncoated pellets

I	Compound 2, Table 1 sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g
	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
V	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
TOTAL	**160 mg**

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [$Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$]	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

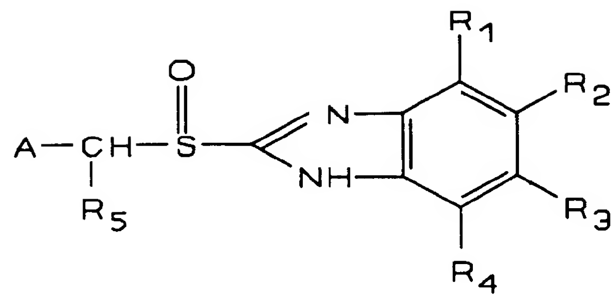
Enteric coating layer

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

Claims

1. The use of core material in the form of small beads or tablets containing as the active ingredient an acid labile compound of the general formula I



wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen,

lower alkyl, lower alkoxy, $-CF_3$,

$$-O-\overset{O}{\overset{\|}{C}}-\text{lower alkyl}$$

or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating, in order to obtain an oral pharmaceutical preparation of said acid labile compound which is stable to discolouration.

2. The use according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

3. The use according to claim 1 wherein the subcoating comprises two or more sub-layers and where the inner layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n ist an integer and less than two.

4. The use according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the microenvironment of the acid labile compound a pH of 7-12.

5. The use according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

6. The use according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. The use according to claim 5 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

8. The use according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. The use according to claim 1 wherein the water content of the final dosage form containing the acid

labile compound does not exceed 1.5 % by weight.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 7178
Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X Y	EP-A-0 173 664 (AKTIEBOLAGET HÄSSLE) * page 2, line 1 - page 3, line 26 * * page 21, line 26 - page 22, line 8 * * page 27, line 1 - line 20 * * page 37, line 19 - page 38, line 12 *	1,4-9 2,3	A61K9/32 A61K9/52 A61K9/54
Y	FR-A-2 272 639 (A.WARREN ET AL.) * page 1, line 1 - line 3 * * page 2, line 19 - page 3, line 20 *	2,3	
D,A	EP-A-0 080 602 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) * page 2, line 1 - line 21 * * page 3, line 6 - line 13 * * page 17, line 10 - line 20 * * page 18, line 1 - line 20 * * page 20, line 4 - line 22 *	1-9	
A	GB-A-760 403 (ABBOT LABORATORIES) * page 1, line 11 - line 34 * * page 2, line 31 - line 70 * * page 6, line 3 - line 18 *	1-9	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	DE-A-3 233 764 (R.P.SCHERER GMBH) * page 6, line 7 - page 7, paragraph 3 * * page 8, last paragraph - page 9, line 1 *	1-9	A61K
A	PATENT ABSTRACTS OF JAPAN vol. 8, no. 106 (C-223)(1543) 18 May 1984 & JP-A-59 020 219 (SHINETSU KAGAKU KOGYO K.K.) 1 February 1984 * abstract *	1-9	
E	EP-A-0 446 961 (TAKEDA CHEMICAL INDUSTRES LTD.) 18 September 1991 * page 2 - page 3, line 6 * * page 7, line 50 - page 8, line 11 * * page 8, line 25 - line 32 * * examples 7,9 * * claims 12,20-27 *	1-9	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13 JULY 1992	MUELLNERS W.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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EUROPEAN SEARCH REPORT

Application Number

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Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)

E	EP-A-0 423 748 (TAKEDA CHEMICAL INDUSTRIES LTD.) 24 April 1991 * claims 11,19--31 *	1-9	

E	EP-A-0 237 200 (TAKEDA CHEMICAL INDUSTRIES LTD.) 16 September 1987 * claims 1,9,10 *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13 JULY 1992	MUELLNERS W.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) Vehicles for oral adminstration of pharmaceutically active acide labile substances.

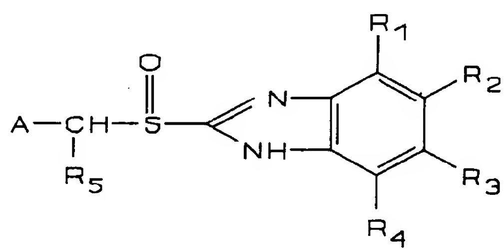
(57) Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances prone to discolouration, containing the acid labile substance where the administration vehicle comprises a core containing said substance together with an alkaline reacting compound or an alkaline salt of said substance optionally mixed with an alkaline reacting compound, adopting the form either of a number of small beads optionally forming a tablet or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

EP 0 565 210 A2

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



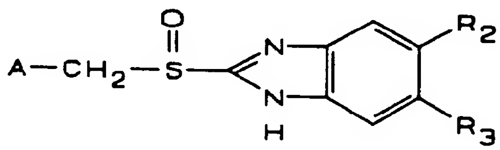
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4, are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

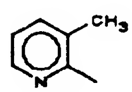
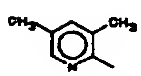
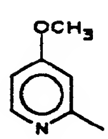
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

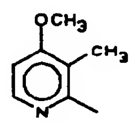
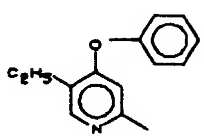
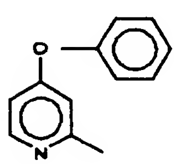
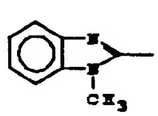
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes for the transformation to the active moiety at pH=2	at pH=7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122

Cont.

Compound No	A	R^2 R^3	Half-life (minutes for the transformation to the active moiety at pH=2	at pH=7
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic

compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3, and R^4, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

$$\text{-O-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-lower}$$

alkyl or halogen and R^5 is H or lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acide labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient

together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

R^1, R^2, R^3 and R^4, which are the same or different and especially

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) -CN
(d) -CHO
(e) $-CF_3$
(f)

$$-\overset{\overset{\displaystyle O}{\|}}{C}-R^{11}$$

(g) $-O-C-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(l) -alkylthio containing 1-6 carbon atoms
(m) $-NO_2$
(n) -akylsulfinyl containing 1-6 carbon atoms
(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 subsituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of theses substituents together form one or two oxo groups

$$(-\overset{\overset{\displaystyle O}{\|}}{C}-),$$

whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same of different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxyalkoxy containing 1-4 carbon atoms
(c) alkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is
(a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is -O- or

$$-\overset{\overset{\displaystyle O}{\|}}{C}- \;;$$

n is 0 or 1;
B is

(a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkynylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c)

$$-\overset{O}{\overset{\parallel}{C}}-R^{9}$$

(d)

$$-(Y)_{m}-(\overset{O}{\overset{\parallel}{C}})_{r}-R^{10}$$

wherein

R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

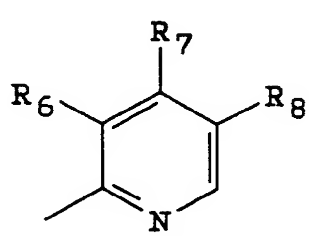
r is 0 or 1;

Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;

R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are
(a) H or
(b) alkyl containing 1-6 carbon atoms;



R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(f) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$
$-O-(CH_2)_p-$
$-S-(CH_2)_v-$
$-CH_2(CH_2)_p-$
$-O-CH=CH-$
$-NH-CH=CH-$

$$-\underset{\displaystyle CH_3}{\underset{|}{N}}-CH=CH-$$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH = 7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less that pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3 \cdot 6MgO \cdot CO_2 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O)$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253 g
	Lactose anhydrous	167 g
	Hydroxypropyl cellulose	25 g
II	Compound 1, Table 1	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5g
	Sodium dihydrogen phosphate	0.1g
	Distilled water	125 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methyl-cellulose	20 g
	Distilled water	400 g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
IV	Cetyl alcohol	3	g
IV	Acetone	540	g
IV	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table 1.

Uncoated pellets

I	Compound 2, Table 1 sodium salt	339	g
I	Mannitol powder	2 422	g
I	Lactose anhydrous	120	g
I	Hydroxypropyl cellulose	90	g
I	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
II	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g

	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
V	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
TOTAL	**160 mg**

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [$Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$]	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

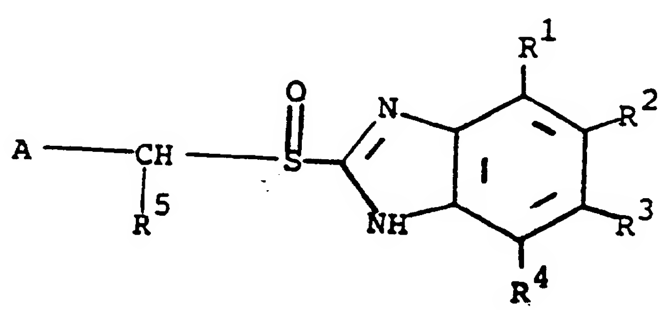
Enteric coating layer

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

Claims

1. Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances, prone to discolouration, of the general formula



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

$$-O-\overset{\overset{\displaystyle O}{\|}}{C}-\text{lower}$$

alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl]-sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylamino-benzyl)-sulfinyl]-benzimidazole as

the active ingredient characterized in that the administration vehicle comprises a core containing the acid labile, active substance, stable to discolouration, together with an alkaline reacting compound or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, either in the form of a number of small beads optionally forming a tablet, or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, a polymeric, water soluble, film-forming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

2. Improvements according to claim 1, wherein the subcoating of the core containing the active substance comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.

3. Improvements according to claim 1 wherein the applied subcoating comprises two or more sub-layers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO.\ CO_2.12H_2O$ or $MgO.Al_2O_3.\ 2SiO_2.nH_2O$, wherein n not is an integer and less than two.

4. Improvements according to claim 1, wherein the alkaline core comprising the acid labile compound contains a pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

5. Improvements according to claim 4 wherein the alkaline compound which the acid labile compound is mixed with comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.\ 12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

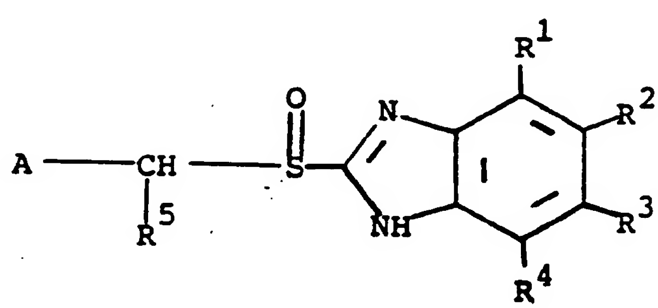
6. Improvements according to claim 1, wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. Improvements according to claim 6 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an otherwise alkaline compound.

8. Improvements according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. Improvements according to claim 1 wherein the dosage form containing the administration vehicle with the acid labile compound has a water content which does not exceed 1.5% by weight.

10. Process for the preparation of vehicles for oral administration of pharmaceutically active acid labile substances, stable to discolouration of the general formula



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

$$-O-\overset{\overset{\displaystyle O}{\|}}{C}-\text{lower}$$

alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole as the active ingredient characterized in that the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, either in the form of a number of small beads optionally forming a tablet, or a tablet as such are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

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(54) **Vehicles for oral administration of a specific pharmaceutically active acid labile substance.**

(57) Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances prone to discolouration, containing omeprazole where the administration vehicle comprises a core containing the omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound, adopting the form either of a number of small beads optionally forming a tablet or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

EP 0 567 201 A2

The present invention is related to a new stable pharmaceutical preparation containing omeprazole for oral use, and to a method for the manufacture of such a preparation.

From e.g. EP-A1-0 005 129 omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)-sulfinyl)-1H-benzimidazole, a potent inhibitor of gastric acid secretion is known. Omeprazole shows a powerful inhibitory action against secretion of gastric juice (Lancet, Nov 27, 1982, p. 1223-1224) and can be used for the treatment of gastric and duodenal ulcers. Omeprazole is, however, susceptible to degradation/transformation in acid reacting and neutral media. The half-life of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH = 7 the half-life of omeprazole is about 14 hours, while at higher pH-values the stability in solution is much better (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). The stability profile is similar in solid phase. The degradation of omeprazole is catalyzed by acidic reacting compounds and is stabilized in mixtures with alkaline reacting compounds. The stability of omeprazole is also affected by moisture and organic solvents.

From what is said about the stability properties of omeprazole, it is obvious that an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

In human pharmacological studies it was found that the rate of release of omeprazole from a pharmaceutical dosage form can influence the total extent of absorption of omeprazole to the general circulation (Pilbrant and Cederberg, Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120). A fully bioavailable dosage form of omeprazole must release the active drug rapidly in the proximal part of the gastrointestinal canal.

In order to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, omeprazole rapidly decomposes by direct or indirect contact with it, with the result that the preparations become rapidly discolored and lose in omeprazole content with the passage of time.

In order to enhance the storage stability the cores which contain omeprazole must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phtalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water of gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alakaline solution will interfere with the enteric coating and eventually dissolve it.

An enteric coated dosage form of omeprazole was reported by Pilbrant and Cederberg, in the above cited Scand. J. Gastroenterology 1985; 20 (suppl. 108) p. 113-120. The publication describes a conventional enteric coated dosage form and states that it has an acceptable storage stability - for clinical studies. It was later found that the stability of this dosage form was insufficient during long-term storage required for a marketed pharmaceutical dosage form.

If a conventional formulation of omeprazole is made, the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

In DE-A1-3046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of omeprazole in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing omeprazole since direct contact between substances such as cellulose acetate phthalate (CAP) and omeprazole causes degradation and discolouration of omeprazole.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of omeprazole in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastrice but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric

coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for omeprazole, where a rapid release of the drug in the small intestine is needed.

DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention.

GB-A-1 485 676 describes a way to obtain a preparation, which effervesces in the small intestine, by enteric coating a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. The formulation cannot be adopted for a pharmaceutical dosage form containing omeprazole, as the presence of an acid in contact with omeprazole in the cores would give a result that omeprazole was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for omeprazole where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing omeprazole.

EP-A-124 495 describes enteric coated granules without subcoating or powder that are filled into hard gelatine capsules or a solution that is filled into soft capsules.

The object of the present invention is to provide an enteric coated dosage form of omeprazole, which is stable to discolouration and which is resistant to dissolution in acid media and which dissolves rapidly in neutral to alkaline media and which has a good stability during long-term storage. The new dosage form is characterized in the following way. Core material in the form of small beads or tablets containing omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating. This/these inner layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability of the dosage form during long-term storage.

Detailed description of the invention

Cores

Omeprazole is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of omeprazole in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each omeprazole particle of not less that $pH = 7$, preferably not less than $pH = 8$, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.\ 2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of omeprazole such as the sodium, potassium, magnesium, calcium etc. salts of omeprazole, which are described in e.g. EP-A2-124 495, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The omeprazole containing alkaline reacting cores must be separated from the enteric coating polymer-(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of omeprazole during the coating process or during storage. The subcoating layer, in the following defined as the

separating layer, also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_36MgO.CO_212H_2O$, $(Mg_6A1_2(OH)_{16}CO_3.4H_2O)$, $MgO.A1_2O_32SiO_2.nH_2O$ or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, methylcellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or polyvinyl acetal diethylaminoacetate. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing omeprazole is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

Enteric coating layer

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions on said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings. The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers. The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colorants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing omeprazole mixed with an alkaline reacting compound or cores containing an alkaline salt of omeprazole optionally mixed with an alkaline reacting compound. The alkaline reacting core material and/or alkaline salt of the active ingredient, omeprazole, enhance the stability of omeprazole. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with an inert reacting water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores form the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and/or the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing omeprazole (enteric coated tablets, capsules or pellets) is kept low, preferably not more than 1.5 % by weight. As a consequence the final package containing hard gelatin capsules filled with enteric coated pellets preferably also contain a desiccant, which reduces the water content of the gelatin shell to a level where the water content of the enteric coated pellets filled in the capsules does not exceed 1.5 % by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the daily dose will be in the range of 1-400 mg of omeprazole.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

The effect of different magnesium compounds was evaluated in the form of enteric coated tablets. Tablet cores were first made by known techniques according to the formulations listed in Table 1, followed by application of separating layers and enteric coating layers shown in Table 2.

Table 1

Formulations for the tablet cores (mg)							
Formulations No.	1	2	3	4	5	6	7
Omeprazol	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Lactose	134.0	119.0	119.0	119.0	118.8	118.5	119.0
Hydroxypropyl cellulose (low substitution	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropyl cellulose	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Na_2HPO_4	-	15.0	-	-	0.2	-	-
Na lauryl sulfate	-	-	-	-	-	0.5	-
MgO	-	-	15.0	-	-	-	-
$Mg(OH)_2$	-	-	-	15.0	15.0	15.0	-
Synthetic hydrotalcite [$A1_2O_3.6MgO.CO_2.12H_2O$]		- -	-	-	-	-	15.0
Total	160.0	160.0	16.0	160.0	160.0	160.0	160.0

Table 2 Formulations for coatings (mg)

Formulation No.	I	II	III	IV
Separating layer (inner):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Magnesium hydroxide	-	-	0.3	-
Synthetic hydrotalcite	-	-	-	0.3
Separating layer (outer):				
Hydroxypropyl cellulose	-	2.0	2.0	2.0
Enteric coating layer:				
Hydroxypropyl methylcellulose phthalate	7.0	7.0	7.0	7.0
Cetyl alcohol	0.5	0.5	0.5	0.5

The tablets thus otained were stored in open form under so called accelerated conditions, that is 40 ° C, and 75 % relative humidity, and the changes in appearance with the passage of time were observed. Storage for six months under these conditions corresponds to storage at normal temperature for three years. This means that high stability sufficient for practical use may be assured if a drug remains intact for about one week under the mentioned conditions. The result is summarized in Table 3. As may be seen from the table, a remarkable stabilizing effect is achieved when a magnesium compound is contained in the inner layer.

Table 3

Stabilizing Effect (Appearance of Preparations)								
Coating Layer		Core material						
		1	2	3	4	5	6	7
I	At the start 60 °C; after 7 days 40 °C; 75% RH; after 7 days	C E F	A D E	A C B	A C B	A C B	A C B	A D E
II	At the start 60 °C; after 7 days 40 °C; 75% RH; after 7 days	A E E	A B D	A A A	A A A	A A A	A A A	A C D
III	At the start 60 °C; after 15 days 40 °C; after 30 days 40 °C; 75% after 15 days	A B A B	A A A A	A A A A	A A A A	A A A A	A A A A	A A A A
IV	At the start 60 °C; after 15 days 40 °C; after 30 days 40 °C; 75% RH; after 15 days	A B A B	A A A A	A A A A	A A A A	A A A A	A A A A	A A A A
A: white, B: brownish white, C: faint brown, D: light brown, E: brown, F: deep brown.								

All the samples evaluated as A (white) in the above table showed no discoloration even on split surfaces. The samples evaluated as B (brownish white) showed little change in appearance, but some discoloration was observed on split surfaces. Table 4 shows the result of a stability test on the omeprazole preparation according to Example 1 (Formulation No 4-IV). The formulation was stored in a closed glass bottle at room temperature for the indicated period of time. This clearly demonstrates that preparations with unusually high stability were obtained.

Table 4

Stability of enteric coated omeprazole preparations (Tablets of Formulation No.4-IV)		
Storage Period	Appearance	Omeprazole Content(%)
At the start of test	White	100.0
1 year at room temp.	White	99.9
2 years at room temp.	White	100.0

Example 2

Uncoated pellets

I	Mannitol powder	16 150	g
	Lactose anhydrous	800	g
	Hydroxypropyl cellulose	600	g
	Microcrystalline cellulose	400	g
II	Omeprazole	2 000	g
	Sodium lauryl sulphate	50	g
	Disodium hydrogen phosphate	80	g
	Distilled water	4 400	g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing suspended omeprazole was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated omeprazole pellets	6 000	g
III	Hydroxypropyl methylcellulose	240	g
	Distilled water	4 800	g

The polymer solution (III) was sprayed on the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric-coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 225 mg, corresponding to 20 mg of omeprazole. 30 capsules were packed in tight containers together with a desiccant.

Example 3

This example illustrates that a variety of polymers can be used for subcoating, e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohols.

Uncoated pellets

I	Mannitol powder	1 620 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Sodium lauryl sulphate	1.0 g
	Disodium hydrogen phosphate	9.3 g
	Distilled water	515 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

III	Uncoated omeprazole pellets	500 g
	Polyvinylpyrrolidone	20 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric-coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	45 g
	Cetyl alcohol	5 g
	Acetone	219 g
	Ethanol	680 g

The enteric-coated pellets were prepared as described in Example 2.

Example 4

Uncoated pellets

I	Mannitol powder	1 610 g
	Lactose anhydrous	80 g
	Hydroxypropyl cellulose	60 g
	Microcrystalline cellulose	40 g
II	Omeprazole	200 g
	Pluronic® F68	10 g
	Disodium hydrogen phosphate	24 g
	Distilled water	450 g

The uncoated pellets were prepared as described in Example 2.

Subcoated pellets

	Uncoated pellets	500 g
III	Polyvinylpyrrolidone	30 g
	Ethanol	400 g

The subcoated pellets were prepared as described in Example 2.

Enteric coated pellets

	Subcoated pellets	500 g
IV	Hydroxypropyl methyl-cellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The enteric coated pellets were prepared as described in Example 2.

Example 5

This example illustrates that a variety of polymers can be used as enteric coating material e.g. cellulose acetate phthalate, poly-(vinyl acetate/vinyl alcohol phthalate), hydroxypropyl methyl cellulose phthalate, poly-(methacrylic acid/methacrylic acid methyl esters), poly-(acrylic acid/methacrylic acid methyl esters). The polymers can be applied with/without plasticizer, e.g. polyethylene glycols, triacetin, dimethyl polysiloxan, Citroflex®, cetyl alcohol, stearyl alcohol, diethyl phthalate.

Enteric-coated pellets can also be manufactured from water-based polymer dispersions, e.g. Aquateric®(FMC Corporation), Eudragit®L 100-55, Coating CE 5142 (BASF).

Uncoated pellets

I	Lactose powder	277 g
	Lactose anhydrous	118 g
	Hydroxypropyl cellulose	25 g
	Colloidal silica	25 g
II	Omeprazole	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	2 g
	Sodium dihydrogen phosphate	0.1 g
	Distilled water	170 g

The uncoated pellets were prepared as described above.

Subcoated pellets

The uncoated pellets were subcoated as described in Example 2.

Enteric coated pellets

	Subcoated pellets	500 g
III	Eudragit®L 500	45 g
	Stearyl alcohol	4.5 g
	Ethanol	1 320 g

The enteric coated pellets were prepared as described above.

Example 6

Formulations with the sodium salt of omeprazole.

Uncoated pellets

I	Omeprazole sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

The preparation was made as described in Example 2 with the exception that the omeprazole sodium salt was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g

IV	Pellets subcoated with III	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500 g
V	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

The preparation of enteric coated pellets was performed as described in Example 2.

Examples 7 and 8

Formulations with the magnesium salt of omeprazole.

Uncoated pellets

		Example No 7	Example No 8
I	Omeprazole magnesium salt	222 g	222 g
	Mannitol powder	1 673 g	1 473 g
	Microcrystalline cellulose	100 g	100 g
	Magnesium hydroxide	-	200 g
II	Sodium lauryl sulphate	5 g	5 g
	Distilled water	500 g	375 g

The preparation was made as described in Example 2 with the exception that the omeprazole salt was added together with the other ingredients in mixture I.

Subcoated pellets

		Examples 7 and 8
	Uncoated pellets	500 g
III	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

The pellets were prepared as described in Example 2.

Enteric coated pellets

		Examples 7 and 8
	Subcoated pellets	500 g
IV	Hydroxypropyl methylcellulose phthalate	57 g
IV	Cetyl alcohol	3 g
IV	Acetone	540 g
IV	Ethanol	231 g

Examples 9 and 10

Manufacture of tablets.

Tablet cores

		Examples No 9	10
I	Omeprazole	400 g	-
I	Omeprazole sodium salt, corresponding to omeprazole 400 g	-	426 g
I	Lactose, anhydrous	1 420 g	1 406 g
I	Polyvinylpyrrolidone, crosslinked	100 g	100 g
I	Sodium carbonate, anhydrous	15 g	-
	Methyl cellulose	12 g	12 g
	Distilled water	200 g	200 g
	Magnesium stearate	30 g	30 g

The powder mixture I was carefully homogenized and granulated by the solution II. The wet mass was dried in a fluidized bed dryer using an inlet air temperature of +50°C for 30 minutes. The dried mixture was then forced through a sieve with an apperture of 0.5 mm. After mixing with magnesium stearate the granulate was tabletted on a tabletting machine using 6 mm punches. The tablet weight was 100 mg.

Subcoating

The tablets containing omeprazole were subcoated with approximately 10 % by weight of hydroxypropyl methylcellulose from a water solution using a perforated coating pan apparatus.

The tablets containing omeprazole sodium salt were subcoated using the dry coating technique. A tablet granulate containing

Lactose anhydrous	4 000 g
Polyvinylpyrrolidone, (PVP)	180 g
Ethanol 95 %	420 g
Magnesium stearate	42 g

was prepared in the following way. The lactose was granulated with a solution of PVP in ethanol and dried. After drying magnesium stearate was admixed.

The granulate mass was dry coated around the tablet cores of Example 9 using a Manesty Dry Cota® tabletting machine. The tablet weight of the dry coated tablets was 475 mg. Each tablet contained 20 mg of omeprazole.

Enteric coating

The subcoated tablets obtained above were enteric coated using the same coating solution:

Hydroxoypropyl methylcellulose phthalate	1 500 g
Cetyl alcohol	105 g
Methylene chloride	15 000 g
Isopropanol	15 000 g
Distilled water	3 150 g

The coating was applied in a perforated coating pan apparatus. An approximate amount of one kg of coating solution was applied for each kg of tablets.

COMPARATIVE EXAMPLES

Examples I, II and III

These examples illustrate that the buffer salt used effects the enteric-coated omeprazole pellets properties when the sub-coating layer is absent. A high amount of buffer salt is needed in order to obtain a long shelf life for the product. At the same time this type of pellets shows inferior acid resistance properties. C.f. also the Example 4 above.

Uncoated pellets

		Examples No I	II	III
I	Mannitol powder	1 610 g	1 610 g	1 610 g
	Lactose anhydrous	80 g	80 g	80 g
	Hydroxypropyl cellulose	60 g	60 g	60 g
	Microcrystalline cellulose	40 g	40 g	40 g
II	Omeprazole	200 g	200 g	200 g
	Pluronic®F68	10 g	10 g	10 g
	Disodium hydrogen phosphate	2 g	8 g	24 g
	Distilled water	450 g	450 g	450 g

The uncoated pellets were prepared as described in Example 2 above.

Enteric coated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methyl-cellulose phthalate	45 g
	Cetyl alcohol	5 g
	Methylene chloride	371 g
	Ethanol	680 g

The coated pellets were prepared as describee in Example 2 above.

Example IV

This formulation is the same as in Example 6 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 6.

Enteric-coated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The enteric coated pellets were prepared as described in Example 2.

Example V

This formulation is the same as in Example 8 above, but no subcoating layer was used.

Uncoated pellets

I	Omeprazole magnesium salt	222	g
	Mannitol powder	1 473	g
	Microcrystalline cellulose	100	g
	Magnesium hydroxide	200	g
II	Sodium lauryl sulphate	5	g
	Distilled water	375	g

The preparation was made as described in Example 8.

Enteric coated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The pellets were prepared as described in Example 2 above.

Properties of the enteric coated pellets

For the preparations according to Examples 2-8 and comparative Examples I-V above one or both of the following studies have been performed.

Acid resistance

The following resistance of the formulations was studied in the following way: The formulations were added to gastric fluid USP (without enzyme), 37° C (paddle) 100 r/min. After 2 hours the actual amount of omeprazole remaining intact in the formulations was determined.

Rate of dissolution in buffer solution

In order to establish the rate of dissolution in the small intestine the formulations were added to a buffer solution. Buffer solution 37° C, USP dissolution apparatus No 2 (paddle), 100 r/min. After 10 or 30 minutes the amount of omeprazole dissolved was determined. The results are presented in the following Table 5.

Table 5

Example No	Omeprazole content mg/g	Acid resistance amount intact omeprazole (%) after 2 hours	% dissolved omeprazole at different pH:s and after 10 or 30 min		
			%	pH	min
2	89.2	96	100	6.8	10
3	90	96	91	6.0	10
4	88	89	*)		
5	82	93	70	7.5	30
6	81.3	87	93	6.8	10
7	91	95	**)		
8	89	98	**)		
I	93	97	*)		
II	92	94	*)		
III	94	58	*)		
IV	86.5	4			
V	91	93	**)		

*) The stability of the formulation was studied during storage in glass bottles also containing a desiccant device. After one month storage at +50 °C the formulation according to Example 4 was virtually intact with no change in appearance or physicochemical characteristics. Pellets according to Example I and II turned brown due to degradation, while the pellets according to Example III retained to original white colour.

**) The formulations according to Examples 7 and 8 were white and not affected by the coating process. The enteric coated pellets according to Example V, where the enteric coating was applied directly on the cores according to Example 8, was discoloured already during the enteric coating process.

Further comparative test

This example demonstrates the effect of the moisture content of the preparations according to the invention on storage stability.

The stability of omeprazole pellets according to the invention was compared with that of omeprazole pellets with higher water content. Omeprazole pellets were prepared according to the invention with a water content of 1 %. Two other portions of the same formulation were conditioned to a water content of 2 % and 5 % respectively. The three formulations, packed in tight containers not containing a desiccant, were stored for one month at + 50 °C. After this time the packages were opened and the pellets were assayed for the amount of omeprazole by HPLC. The formulation according to the invention had an omeprazole content of 98.5 % of the initial value. The other two formulations with at water content of 2 and 5 % respectively were totally degraded and had only trace amounts of intact omeprazole.

DISCUSSION

From the results given in Table 5 it can be seen that formulations containing omeprazole with acceptable acid resistance can be prepared by using a conventional enteric coating technique (see for instance Examples I, II and V). However, it is also obvious that the storage stability of the formulations according to Examples I, II and V is not acceptable, since a discolouration, showing a degradation of omeprazole, occurs during short storage at an elevated storage temperature (Examples I and II) or already during the enteric coating process (Example V).

If the amount of alkaline substances in the cores is increased to a level where omeprazole has an acceptable storage stability (Example III) or if an alkaline reacting salt of omeprazole is used in the preparation of the cores (Example IV), then, without the separating layer of the invention, the resistance to dissolution in acid media becomes unacceptably low and much or all of the active substance will degrade already in the stomach and thus, it has no effect on the gastric acid secretion.

When the preparation is carried out to the invention as for instance in Example 4, a good resistance towards gastric juice as well as a good stability during long-term storage is obtained. This is in contrast with the formulations in Examples I, II and III where either an acceptable acid resistance or an acceptable storage stability can be achieved - but not both. The same comparison can be made between the formulations according to Examples 7 and 8 according to the invention and the formulation according to Example V, where the separating layer was omitted. Examples 7 and 8 differ in that a buffering substance, magnesium hydroxide, has been included in the cores of Example 8. This further improves the acid resistance as well as the storage stability of Example 8 in comparison with Example 7.

The further comparative test shows the great importance of a low water content in the preparations.

Thus, in order to prepare pharmaceutical formulations of omeprazole for oral use, which exert good stability during long-term storage as well as good stability during the residence in the stomach after administration, the preparation is made in the following way:

a) Omeprazole together with an alkaline reacting compound or compounds or an alkaline reacting salt of omeprazole optionally mixed with alkaline reacting compound are included in the core material.

b) The core material is subcoated with one or more inert, in water soluble or in water rapidly disintegrating layers, which separate the alkaline reacting core from the enteric coating. The subcoating layer may optionally contain pH-buffering compounds.

c) The subcoated cores are coated with an acid insoluble enteric coating, optionally containing plasticizers.

Biopharmaceutical studies

The hard gelatin capsules according to Example 2 were administered to 12 healthy, young male volunteers in the following way:

The volunteers came to the laboratory in the morning after having abstained from food since 10 p.m. the night preceeding the experimental day. A zero time blood sample was taken. One omeprazole capsule according to Example 2 was administered together with 150 ml of tap water. Further blood samples were taken during the day.

In another experiment the same volunteers were administered 20 mg of omeprazole in the form of a suspension of micronized omeprazole in a sodium bicarbonate water solution. In order to reduce the

degradation of omeprazole in the stomach to a minimum, solid bicarbonade solution was given to the subjects just before the administration of the omeprazole suspension and at further four times with a 10-minutes interval after the drug intake. The concentration of omeprazole in blood plasma was assayed by high pressure liquid chromatography (Persson, Lagerström and Grundevik. Scand J Gastroenterol 1985, 20, (suppl 108), 71-77. The mean plasma concentrations are given in Table 6.

Table 6

The plasma concentrations (µmol/l) after 20 mg single oral doses of omeprazole given as hard gelatin capsules according to Example 2 and as a suspension of micronized omeprazole in sodium bicarbonate solution.

Time (min)	Capsules	Suspension
10		0.84
20		0.90
30	0.03	0.84
45		0.64
60	0.22	0.44
90	0.36	0.24
120	0.39	0.13
150	0.29	
180	0.20	0.04
210	0.10	
240	0.05	0.01
300	0.02	0
360	0.01	
420	0	

Although the plasma concentration peak at different times, the two formulations are bioequivalent. The mean relative bioavailability of the capsules in comparison with the suspension was 85 % +23 % (S.D.). The comparison was based on the total area under individual plasma concentration versus times curves.

Thus, by preparing capsules according to the invention it is possible to obtain a preparation with the same bioavailability as a suspension containing the same amount to micronized active compound. It is, however, to be noticed that when the suspension is administered, the patients must also be given sodium bicarbonate solution frequently in order to minimize pre-absorption degradation of omeprazole in the stomach.

Claims

1. Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances prone to discolouration, containing omeprazole characterized in that the administration vehicle comprises a core containing the omeprazole together with an alkaline reacting compound or an alkaline salt

of omeprazole optionally mixed with an alkaline reacting compound, adopting the form either of a number of small beads optionally forming a tablet or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

2. Improvements according to claim 1, wherein the subcoating of the core containing omeprazole comprises hydroxypropyl methycellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.

3. Improvements according to claim 1 wherein the applied subcoating comprises two or more sub-layers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.\ 2SiO_2.nH_2O$, wherein n not is an integer and less than two.

4. Improvements according to claim 1 wherein the omeprazole containing core comprises omeprazole mixed with a pH-buffering alkaline compound rendering to the microenvironment of the omeprazole a pH of 7-12.

5. Improvements according to claim 4 wherein the alkaline compound which the omeprazole is mixed with comprises one or more magnesium oxide, hydroxide or carbonate, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.\ 12\ H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

6. Improvements according to claim 4 wherein the alkaline core comprises an alkaline salt of omeprazole such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. Improvements according to claim 4 wherein the alkaline core comprises an alkaline salt of omeprazole mixed with an otherwise alkaline compound.

8. Improvements according to claim 1 wherein the enteric outer coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. Improvements according to claim 1 wherein the dosage form containing the administration vehicle with omeprazole has a water contents which does not exceed 1,5% by weight.

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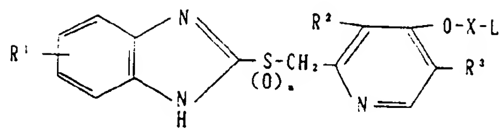
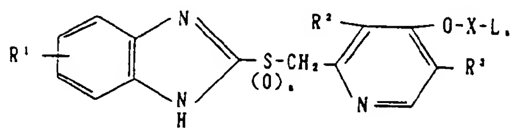
(54) **USE OF PYRIDINE COMPOUND AS SELECTIVE DRUG AND NOVEL PYRIDINE COMPOUND.**

(57) A compound of general formula (I) and its salt, wherein each symbol is as defined in the specification, and a new compound of general formula (II) and its salt which are included in the above compound and its salt. These compounds have an excellent selective sterilization effect on the bacteria belonging to the genus Helicobacter and are useful for preventing the recrudescence and recidivation of ulcers, suppressing vomit, preventing and treating non-ulcer dyspepsia, preventing and treating tumors, and also as an antiulcer drug.

EP 0 567 643 A1



(I)



(II)

TECHNICAL FIELD

The present invention relates to a use of a novel or known pyridine compound as a selective drug, and to a novel pyridine compound useful for the prevention and treatment of disorders in the digestive tract.

BACKGROUND ART

The bacterium belonging to the genus *Campylobacter* which is a Gram-negative microaerophile was found as a bacterium causing diarrhea and miscarriage in domestic animals. With regard to humans, there have been known *Campylobacter jejuni* and *Campylobacter coli* as bacteria causing bacterial enteritis. In 1983, Warren et al. reported involvement of the infection of *Campylobacter pylori* (current name: *Helicobacter pylori*, hereinafter the current name is used) in gastritis, and there have been done a multitude of studies and presented many reports ever since. Actually, *Helicobacter pylori* has been found, at high frequencies, in antral gastritis tissues to be combined with chronic gastritis, or gastric ulcer and duodenal ulcer.

In recent years, there are increasing numbers of reports teaching that duodenal ulcer, chronic gastritis, and non-ulcer dyspepsia can be healed by the antibacterial action on *Helicobacter pylori*, and that recurrence and relapse of the diseases are few. For example, of the 73 patients out of the 75 patients with relapsed or resistant duodenal ulcer, who were initially treated with ranitidine and then with triple administration of colloidal bismuth subcitrate, tetracycline, and metronidazole for 4 weeks, 71 patients did not suffer from infection of *Helicobacter pylori* or relapse of the ulcer at 1 year later. In the second year, all 57 patients who underwent endoscopy did not carry the bacterium nor did they suffer from relapse of the ulcer. At three years from the treatment, 34 patients underwent an examination, and the bacterium was not found in 33 of them, with no evidence of relapse of duodenal ulcer in all of the 34 patients. In contrast, the percent relapse in case of the sole treatment with ranitidine was 70-90% (SCRIP, No. 1549, p. 24, Sep. 14, 1990). The Lancet, vol. 335, p. 1599 (1990) reports that of the 48 child patients treated with antibiotics to exert antibacterial action on *Helicobacter pylori*, only one child suffered from relapsed duodenal ulcer after the average two-year follow up examination, and the patients who did not suffer from relapse carried no *Helicobacter pylori*. The Lancet, vol. 336, p. 755 (1990) reports the results of a 4-week treatment of 61 *Helicobacter pylori*-positive, duodenal ulcer patients, who were divided into two groups (a group administered with ranitidine and a group combinedly administered with ranitidine and oxacillin), in terms of percent relapse after 12 months, wherein the group administered with ranitidine showed 86% of relapse (*Helicobacter pylori* tested positive in all patients) and the group administered combinedly showed 37% of relapse (*Helicobacter pylori* tested positive in 16 patients out of 32). Further, The Lancet, No. 8626/8627, p. 1502 (1988) reports that the administration of antacid, metoclopramide, domperidone, etc. was ineffective against vomiting observed in the patients with *Helicobacter pylori*-related gastritis, whereas antibacterial treatment on *Helicobacter pylori* could suppress the vomiting. Also, *Helicobacter pylori* is said to induce tumor.

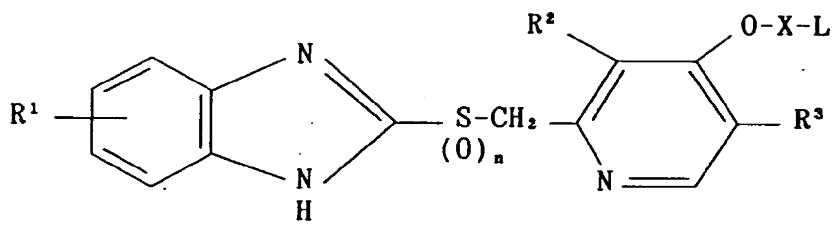
It should be noted that the bismuth compounds have low potency in the antibacterial action on *Helicobacter pylori*, and accompany vomiting and central side effects. In addition, antibiotics exert influence on other bacteria as well, and the administration on a long term basis is not desirable.

As the situation stands, development of a useful pharmaceutical usable for the prophylaxis and treatment of various diseases caused by *Helicobacter pylori* has been demanded. For inhibiting recurrence and relapse of ulcer, as well as suppression of vomiting, a novel pharmaceutical having antiulcer activity, gastric acid secretion-suppressing activity, gastrointestinal cell-protecting activity, and antidiarrhea activity besides the antibacterial activity on the bacteria belonging to the genus *Helicobacter*, has a great demand for development.

DISCLOSURE OF THE INVENTION

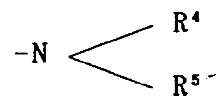
The present invention is as follows.

(1) An agent for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*, comprising a pyridine compound of the formula

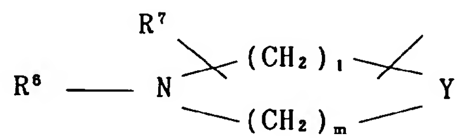


(I)

wherein R^1 is hydrogen, halogen, alkyl, alkoxy, alkoxycarbonyl, or haloalkyl, R^2 and R^3 are the same or different and each is hydrogen, halogen or alkyl, n is 0, 1 or 2, X is single bond or alkylene, and L is alkoxy, a group of the formula



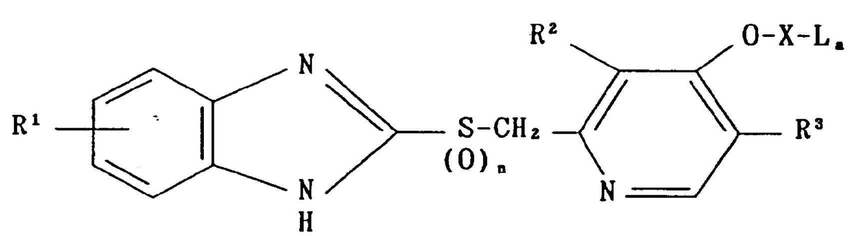
wherein R^4 and R^5 are the same or different, and each is hydrogen, alkyl, acyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, or furylalkyl, thienylalkyl or pyridylalkyl which may be substituted, or R^4 and R^5 together with the adjacent nitrogen atom form a heterocyclic ring which may be condensed, or a group of the formula



wherein R^6 is hydrogen, alkyl, acyl, phenylalkyl, or substituted phenylalkyl, R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroarylalkyl, or substituted heteroarylalkyl, Y is methylene, oxygen or sulfur, and l and m are the same or different and each is 0, 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

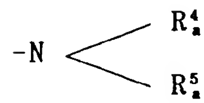
(2) An agent for inhibiting recurrence and relapse of ulcer, a suppressant of vomiting, or an agent for the prevention and treatment of non-ulcer dyspepsia, comprising the compound of the formula (I) or a pharmaceutically acceptable salt thereof.

(3) A pyridine compound of the formula

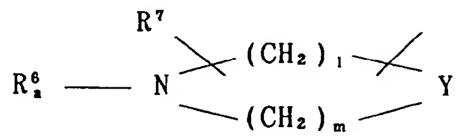


(II)

wherein R^1 is hydrogen, halogen, alkyl, alkoxy, alkoxycarbonyl, or haloalkyl, R^2 and R^3 are the same or different and each is hydrogen, halogen or alkyl, n is 0, 1 or 2, X is single bond or alkylene, and L_a is a group of the formula



wherein R_a^4 is alkyl and R_a^5 is furylalkyl, thienylalkyl or pyridylalkyl which may be substituted, or a group of the formula



wherein R_a^6 is phenylalkyl or substituted phenylalkyl, R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroarylalkyl, or substituted heteroarylalkyl, Y is methylene, oxygen or sulfur, and l and m are the same or different and each is 0, 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

(4) An agent for the prevention and treatment of disorders in the digestive tract, comprising the compound of the formula (II) or a pharmaceutlcally acceptable salt thereof.

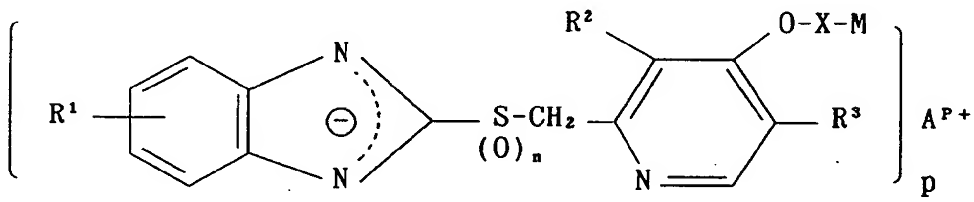
(5) A method for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*, or for inhibiting recurrence and relapse of ulcer, or for suppressing vomiting, or for the prevention and treatment of non-ulcer dyspepsia, comprising administration of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, or the compound of the formula (II) or a pharmaceutically acceptable salt thereof.

(6) Use of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, or the compound of the formula (II) or a pharmaceutically acceptable salt thereof for the production of an agent for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*, or an agent for inhibiting recurrence and relapse of ulcer, or a suppressant of vomiting, or an agent for the prevention and treatment of non-ulcer dyspepsia.

In the present specification, halogen means chlorine, bromine, fluorine or iodine; alkyl means alkyl having 1 to 20 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, octyl, decyl, dodecyl, octadecyl or eicosyl; alkoxy means alkoxy having 1 to 20 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, octyloxy, decyloxy, dodecyloxy, octadecyloxy or elcosyloxy; alkylene means alkylene having 1 to 8 carbon atoms such as methylene, ethylene, methylmethylene, trimethylene, propylene, isopropylidene, tetramethylene, hexamethylene or 2-ethylhexamethylene; alkoxycarbonyl means alkoxycarbonyl having 1 to 20 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, decyloxycarbonyl, dodecyloxycarbonyl, octadecyloxycarbonyl or eicosyloxycarbonyl; haloalkyl means haloalkyl having 1 to 4 carbon atoms such as trifluoromethyl, 2,2,2-tifluoroethyl, 2,3,3-trifluoropropyl, 1,1,2,2-tetrafluoroethyl or 2,2,3,3-tetrafluoropropyl; phenylalkyl means alkyl having 1 to 8 carbon atoms substituted by phenyl such as benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 6-phenylhexyl or 8-phenyloctyl; acyl means alkanoyl having 1 to 5 carbon atoms such as acetyl, propionyl, isopropionyl, butyryl, pivaloyl, valeryl and benzoyl; substituent for substituted phenyl, substituted phenylalkyl, furylalkyl, thienylalkyl and pyridylalkyl means 1 to 3 groups selected from the group consisting of halogen, alkyl, alkoxy, haloalkyl, hydroxyl, nitro and amino; heterocyclic ring formed with the adjacent nitrogen atom, which may be condensed includes 1-pyrrolidinyl, piperidino, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-aralkyl-1-piperazinyl, 4-substituted aralkyl-1-piperasinyl, 4-alkyl-1-homopiperazinyl, 4-acyl-1-homopiperazinyl, morpholino, thiomorpholino, 2-oxo-1-pyrrolidinyl, 2,4-dioxo-1-pyrrolidinyl, 2-oxo-1-piperidinyl, isoindolin-2-yl, 1,2,3,4-tetrahydroquinolin-1-yl, and 1,2,3,4-tetrahydroisoquinolin-2-yl (these isolndollne ring and 1,2,3,4-tetrahydro(iso)-quinoline ring may be substituted by 1 to 3 substituents optionally selected from the group consisting of halogen, alkyl, alkoxy, haloalkyl, hydroxyl, nitro, amino and oxo); heteroarylalkyl means, for example, 2-thenyl, 3-thenyl, furfuryl, 3-furylmethyl, 2-, 3- or 4-pyridylmethyl, or 2-pyrimidinylmethyl; and the substituent for substituted heteroarylalkyl means 1 to 3 groups selected from the group consisting of halogen, alkyl, alkoxy, haloalkyl, hydroxyl, nitro and amino.

The compound of the formula (I) of the present invention comprises various isomers. The present invention encompasses one of these isomers or a mixture of such isomers.

The pharmaceutically acceptable salt of the compound of the formula (I) includes salts of the formula



(III)

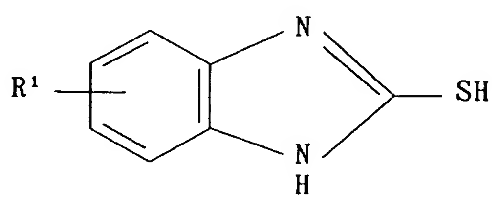
wherein p is an integer of 1 to 4, A^{p+} is Li^{+}, Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, $A\ell^{3+}$, Ti^{4+}, $N^{+}(R)_4$ (wherein R is alkyl having 1 to 4 carbon atoms) or $C^{+}(NH_2)_3$, M is the definition L or L_a, and other symbols are as defined above.

As the compound of the formula (III), particularly preferred are sodium salt, calcium salt, and magnesium salt.

The compound of the present invention exists as hydrates (e.g. semihydrate, monohydrate, sesquihydrate) or as various solvates, all of which are also encompassed in the present invention.

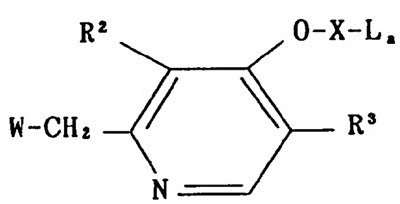
The compound of the formula (I) can be prepared by a known method such as the method disclosed in Japanese Patent Unexamined Publication No. 6270/1989 or International Publication No. WO89/00566.

The compound of the formula (II) can be prepared in a similar manner as in the following, in which a compound of the formula



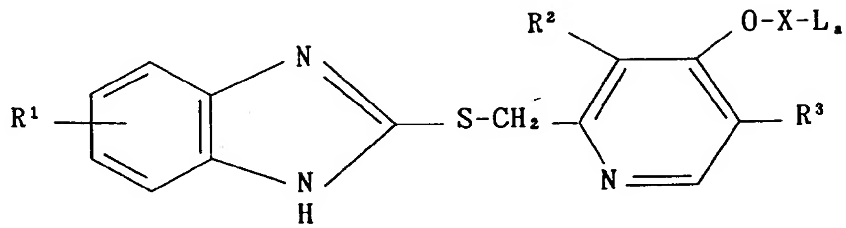
(IV)

wherein R^1 is as defined above, is reacted with a compound of the formula



(V)

wherein W is reactive atom or a group such as halogen or sulfonyloxy (e.g. methanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy), and other symbols are as defined above, or preferably an acid addition salt thereof, to give a compound of the formula



(VI)

wherein each symbol is as defined above, which is then subjected to oxidation.

The reaction of the compound (IV) and compound (V) usually proceeds in an inert solvent such as water, methanol, ethanol, dimethylformamide, or a mixed solvent thereof, preferably aqueous ethanol, in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium metal, triethylamine, or pyridine at a temperature between about 0 °C and the boiling point of the solvent used, preferably from 20 to 80 °C for about 10 minutes to 24 hours, preferably for 30 minutes to 3 hours.

The oxidizing agent to be used for the oxidation includes, for example, perbenzoic acid, m-chloroperbenzoic acid, peracetic acid, trlfluoroperacetic acid, permaleic acid, sodium bromite, sodium hypochlorite, hydrogen peroxide, tert-butyl hydroperoxide, and cumene hydroperoxide. The reaction usually proceeds in an inert solvent such as water, dichloromethane, chloroform, tetrahydrofuran, dioxane, dimethylformamide, or a mixed solvent thereof, in the presence of an organic acid such as formic acid, acetic acid, proplonic acid, butyric acid, maleic acid, fumaric acid, malonic acid, succinic acid, benzoic acid, m-chlorobenzoic acid, p-nitrobenzoic acid, or phthalic acid at a temperature between about -70 °C and the boiling point of the solvent used, usually from -50 °C to room temperature, preferably from -20 °C to 0 °C for about 5 minutes to 24 hours, preferably for about 5 minutes to 20 hours; or proceeds in water or an alcohol solvent such as ethanol, methanol, or propanol, in the presence of an alkali such as alkali hydroxide (e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide) at a temperature between about -70 °C and the boiling point of the solvent used, usually from -50 °C to room temperature, preferably from -20 °C to 10 °C for about 5 minutes to 20 hours, preferably for 1 hour to 10 hours.

The compound (I) thus synthesized can be separated and purified by known means such as recrystallization and column chromatography.

The optical isomers of the compounds (I) and (II) can be produced by subjecting reaction products to fractional crystallization, or by conducting the aforementioned reactions using the starting materials previously subjected to optical resolution.

The salt compound of the formula (III) can be obtained by reacting a compound (I) or (II) with a base corresponding thereto.

Examples of compound (I), compound (II) and pharmaceutically acceptable salts thereof include the following, to which the present invention is not limited.

Compound 1 : 2-[3-methyl-4-(1-methyl-2-piperidyl)methoxy-2-pyridyl]methylthio-1H-benzimidazole, m.p. 125-126 °C

Compound 2 : 2-[3-methyl-4-(3-morpholinopropoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 148-150 °C (decomposition)

Compound 3 : 2-[3-methyl-4-(2-piperidinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 105-110 °C

Compound 4 : 2-[3-methyl-4-(2-(2-oxo-1-pyrrodinyl)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 64-65 °C

Compound 5 : 2-[3-methyl-4-(2-morpholinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}H-NMR ($CDCl_3$) : δ (ppm) = 2.28 (s, 3H), 2.50-2.70 and 3.68-3.84 (each m, 8H), 2.88 (t, 2H), 4.20 (t, 2H), 4.40 (s, 2H), 6.76 and 8.34 (each d, 2H), 7.08-7.26 and 7.44-7.60 (each m, 4H)

Compound 6 : 2-[3-methyl-4-(3-piperidinopropoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 114-115 °C (decomposition)

Compound 7 : 5-methoxy-2-[3-methyl-4-(2-morpholinoethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}H-NMR ($CDCl_3$) : δ (ppm) = 2.25 (s, 3H), 2.5-2.7 (m, 4H), 2.87 (t, 2H), 3.6-3.85 (m, 4H), 3.85 (s, 3H), 4.2 (t, 2H), 4.4 (s, 2H), 6.7-6.9 (m, 2H), 7.05 (d, 1H), 7.4 (d, 1H), 8.35 (d, 1H)

Compound 8 : 5-methoxy-2-[3-methyl-4-(2-N-benzyl-N-methylamino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 121-122 °C

Compound 9 : 2-[3-methyl-4-(2-(N-methyl-N-(2-phenylethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}H-NMR ($CDCl_3$) : δ (ppm) = 2.24 (s, 3H), 2.44 (s, 3H), 2.60-2.84 (m, 4H), 2.92 (t, 2H), 4.12 (t, 2H), 4.39 (s, 2H), 6.72 and 8.32 (each d, 2H), 7.10-7.35 and 7.40-7.60 (each m, 9H)

Compound 10 : 2-[3-methyl-4-(2-(N-methyl-N-(3-phenylpropyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}H-NMR ($CDCl_3$) : δ (ppm) = 1.64-2.10 (m, 2H), 2.22 (s, 3H), 2.39 (s, 3H), 2.52 and 2.68 (each t, 4H), 2.86 (t, 2H), 4.11 (t, 2H), 4.40 (s, 2H), 6.72 and 8.32 (each d, 2H), 7.04-7.40 and 7.40-7.70 (each m, 9H)

Compound 11 : 2-[3-methyl-4-(2-(N-benzyl)-N-ethylamino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}N-NMR ($CDCl_3$) : δ (ppm) = 1.10 (t, 3H), 2.14 (s, 3H), 2.68 (q, 2H), 2.92 (t, 2H), 3.70 (s, 2H), 4.04 (t, 2H), 4.36 (s, 2H), 6.62 and 8.30 (each d, 2H), 7.00-7.64 (each m, 9H)

Compound 12 : 2-[3-methyl-4-(2-(N-benzyl-N-propylamino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

^{1}H-NMR ($CDCl_3$) : δ (ppm) = 0.90 (t, 3H), 1.54 (m, 2H), 2.24 (s, 3H), 2.56 (t, 2H), 2.91 (t, 2H), 3.69 (s, 2H), 4.04 (t, 2H), 4.36 (s, 2H), 6.62 and 8.28 (each d, 2H), 6.96-7.64 (each m, 9H)

Compound 13 : 2-[3-methyl-4-(2-(N-methyl-N-(4-methylbenzyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 99-102 °C

Compound 14 : 2-[3-methyl-4-(2-(N-(4-chrolobenzyl)-N-methylamino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 15 : 2-[3-methyl-4-(2-(N-(4-bromobenzyl)-N-methylamino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 110-112 °C (decomposition)

Compound 16 : 2-[3-methyl-4-(2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 17 : 2-[3-methyl-4-(2-(N-benzyl-N-methylamino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole ½ magnesium salt, m.p. 114-120 °C (decomopsition)

Compound 18 : 2-[3-methyl-4-(2-(N-methyl-N-(4-methylbenzyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole ½ magnesium salt, m.p. 127-132 °C (decomposition)

Compound 19 : 2-[3-methyl-4-(2-(N-(4-bromobenzyl)-N-methylaminoethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole ½ magnesium-salt, m.p. 119-124 °C (decomposition)

Compound 20 : 2-[3-methyl-4-(2-(1,2,3,4-tetrahydroisoquinolin-2-yl)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole ½ magnesium salt, m.p. 173-184 °C (decomposition)

Compound 21 : 2-[3-methyl-4-(2-(N-benzyl-N-methylamino)ethoxy)-2-pyridyl]methylsulfonyl-1H-benzimidazole, m.p. 137-139 °C (decomposition)

Compound 22 : 2-[3-methyl-4-(2-N-methyl-N-(4-methylbenzyl)amino)ethoxy)-2-pyridyl]methylsulfonyl-1H-benzimidazole, m.p. 137-139 °C (decomposition)

Compound 23 : 2-[3-methyl-4-(1-benzyl-4-piperidyl)oxy-2-pyridyl]methylthio-1H-benzimidazole

Compound 24 : 2-[3-methyl-4-(1-benzyl-4-piperidyl)oxy-2-pyridyl]methylsulfinyl-1H-benzimidazole½ magnesium salt, dihydrate

Compound 25 : 2-[3-methyl-4-(1-benzyl-2-piperidyl]methoxy-2-pyridyl]methylthio-1H-benzimidazole, m.p. 82-85 °C

Compound 26 : 2-[3-methyl-4-(2-(N-methyl-N-(2-thienylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole, m.p. 104-108 °C (decomposition)

compound 27 : 2-[3-methyl-4-(2-(N-methyl-N-(2-thienylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole ½ magnesium salt dihydrate

Compound 28 : 2-[3-methyl-4-(1-benzyl-2-piperidyl)methoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole$^1/_2$magnesium salt 5/2 dihydrate

Compound 29 : 2-[3-methyl-4-(2-(N-methyl-N-(3-thienylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 30 : 2-[3-methyl-4-(2-(N-methyl-N-(3-thienylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole

Compound 31 : 2-[3-methyl-4-(2-(N-methyl-N-(3-methyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylthio-1H-benzimidazole

Compound 32 : 2-[3-methyl-4-(2-(N-methyl-N-(3-methyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylsulfinyl-1H-benzimidazole

Compound 33 : 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylthio-1H-benzimidazole

Compound 34 : 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylsulfinyl-1H-benzimidazole

Compound 35 : 2-[3-methyl-4-(2-(N-methyl-N-(5-ethyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 36 : 2-[3-ethyl-4-(2-(N-methyl-N-(5-ethyl-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylsulfinyl-1H-benzimidazole

Compound 37 : 2-[3-methyl-4-(2-(N-methyl-N-(5-bromo-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylthio-1H-benzimidazole

Compound 38 : 2-[3-methyl-4-(2-(N-methyl-N-(5-bromo-2-thienylmethyl)amino)ethoxy)-2-pyridyl]-methylsulfinyl-1H-benzimidazole

Compound 39 : 2-[3-methyl-4-(2-(N-methyl-N-(2-furylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 40 : 2-[3-methyl-4-(2-(N-methyl-N-(2-furylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole

Compound 41 : 2-[3-methyl-4-(2-(N-methyl-N-(3-furylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 42 : 2-[3-methyl-4-(2-(N-methyl-N-(3-furylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole

Compound 43 : 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-furylmethyl)amino)ethoxy)-2-pridyl]methylthio-1H-benzimidazole

Compound 44 : 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-furylmethyl)amino)ethoxy)-2-pyridyl]-methylsulfinyl-1H-benzimidazole

Compound 45 : 2-[3-methyl-4-(2-(N-methyl-N-(2-pyridylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole

Compound 46 : 2-[3-methyl-4-(2-(N-methyl-N-(2-pyridylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole

Compound 47 : 2-[3-methyl-4-(3-methyl-4-(3-methoxypropoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole sodium salt

The compound (I) shows selective antibacterial activity on the bacteria belonging to the genus *Helicobacter* represented by *Helicobacter pylori*. Accordingly, the compound (I) of the present invention is effective in the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*. That is, the compound of the present invention is usable for the prevention and treatment of various diseases in mammals inclusive of human, which are caused by the bacteria belonging to the genus *Helicobacter*, for inhibiting recurrence and relapse of ulcer, for suppressing vomiting, for the prevention and treatment of non-ulcer dyspepsia, or for the prevention and treatment of tumor. In addition, the novel compound (II) of the present invention has antiulcer activity, gastric acid secretion-suppressing activity, gastrointestinal cell-protecting activity, and antidiarrhea activity besides the aforementioned activity, and is useful for the prevention and treatment of disorders in the digestive tracts such as gastric ulcer, duodenal ulcer, gastritis, diarrhea, and colitis. Also, the compound is characterized by low toxicity and small rise of gastrin value in blood.

When using the compound (I), (II) or a salt thereof as a pharmaceutical, it can be administered generally in the form of a pharmaceutical preparation comprising said compound per se or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carrier, upon mixing same with additives such as excipients, carriers, diluents, solubilizing agents, etc. and formulation into the form of capsules, tablets (including sugar-coated tablets and film-coated tablets), granules, injections or transfusions. In the case of oral administration, the dose is about 0.01-20 mg/kg/day, preferably 0.1-4 mg/kg/day for an adult, though it may vary depending on symptoms, age, resistance to drug, etc. of patients.

Experiment 1

Antibacterial activity (*in vitro*) of the active ingredient compounds of the invention against *Helicobacter pylori* CPY-4, CPY-13, CPY-23 and ATCC 43504 were determined by the agar plate dilution method described below.

The test strains were incubated microaerobically at 37°C for 72 hours on agar supplemented with 5% horse serum and were diluted with Brucella broth (BBL) to about 10^6 CFU/ml. Each bacterial suspension was applied to the Brucella-blood agar plate containing twofold serial dilutions of the test compounds by a multipoint inoculator (Microplanter). The plates were incubated at 37°C for 2 days in the presence of 10% CO_2. The MIC was defined. The results are shown in Table 1.

Table 1

Test compound	CPY-4	MIC (μg/ml) CPY-13	CPY-23	ATCC 43504
1	1.56	1.56	3.13	3.13
2	0.39	0.39	0.39	0.78
3	1.56	1.56	1.56	6.25
4	0.78	0.78	0.78	3.13
5	0.012	0.012	0.05	0.05
6	3.13	3.13	3.13	6.25
7	0.39	0.39	0.39	0.78
8	0.39	0.39	0.39	0.39
9	0.10	0.10	0.20	0.20
10	0.20	0.20	0.20	0.20
11	0.025	0.05	0.10	0.10
12	0.20	0.39	0.39	0.78
13	0.05	0.10	0.39	0.20
14	0.025	0.10	0.20	0.10
15	0.10	0.10	0.05	0.10
16	0.012	0.012	0.05	0.012
17	0.025	0.025	0.10	0.05
18	0.10	0.10	0.10	0.20
19	0.05	0.10	0.05	0.10
20	0.012	0.012	0.012	0.012
21	0.39	0.78	0.39	1.56
22	0.78	0.78	0.78	1.56
23	0.05	0.05	0.20	0.20
24	0.05	0.05	0.20	0.10
25	0.39	0.39	0.39	0.39
26	0.05	0.025	0.20	0.10
27	0.05	0.05	0.10	0.10
28	0.39	0.78	0.39	0.78

Experiment 2

The test strains were preincubated in Muller-Hinton broth and were diluted with the same broth to about 10^6 CFU/ml. 5 μl of an inoculum was inoculated onto an agar containing twofold serial dilutions of the test compound. The plates were incubated at 37°C for 18 hours. The minimum Inhibitory concentration (MIC) was defined as the lowest concentration of the test compound inhibiting formation of bacterial colony. The results are shown in Table 2.

Table 2

Test bacteria	MIC (μg/ml)	
	Compound 17	Compound 20
Staphylococcus aureus FDA 209P	100	>100
Staphylococcus epidermidis ATCC 12228	100	100
Enterococcus faecalis LS-101	>100	>100
Bacillus subtilis PCI 219	>100	>100
Escherichia coli NIHJ JC-2	>100	>100
Klebsiella pneumoniae DT	>100	>100
Proteus vulgaris IFO 3988	>100	>100
Acinetobacter calcoaceticus IFO 13006	>100	>100
Pseudomonas aeruginosa IFO 12582	>100	>100
Candida albicans IFO 1060	>100	>100

As is eveident from Table 2, the compound of the formula (I) had no effect on Gram-positive bacteria, Gram-negative bacteria and fungi.

Experiment 3

Acid secretion in the gastric lumen-perfused rats

Experiments were performed according to the method described by Ghosh et al. (Br. J. Pharmacol. *13*. 54, 1958). Wistar rats were deprived of food for 20 hours and anesthetized with urethane (1.5 g/kg, s.c.). A polyethylene tube canula for introducing perfusion liquid and another tube for draining perfusate were inserted into the stomach. The stomach was perfused at a flow rate of 7 ml/min with warmed saline (37°C) and perfusate was collected for acid measurement. Acid secretion induced by histamine hydrochloride (1 mg/kg, i.v.) every hour was measured by antonomic titration of the perfusate to pH 7.0. Test compounds were administered intravenously 5 min before histamine hydrochloride injection. The results are shown in Table 3 as ED_{50} values; the doses caused 50% inhibition of gastric acid secretion.

Table 3

Test compound (Example No.)	ED_{50} (mg/kg, i.v.)
2	1.5
5	0.9
6	1.7

The present invention is hereinbelow detailedly described by illustrating Examples and Formulation Examples. It should be understood that the present invention is not limited to them.

Example 1

2-Chloromethyl-3-methyl-4-[(1-benzyl-4-piperidyl)oxy]pyridine dihydrochloride (8.7 g) was added to 120 ml of ethanol containing 2-mercaptobenzimidazole (3.6 g) and 13.5% sodium hydroxide (23 ml), and the mixture was stirred at room temperature for 1 hour. After the completion of the reaction, ethanol was distilled off, and water was added to the residue. The precipitated crystals were collected by filtration, and recrystallized from ethyl acetate to give 2-[3-methyl-4-(1-benzyl-4-piperidyl)oxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 23), m.p. 148 °C.

Example 2

To 2-[3-methyl-4-(1-benzyl-4-piperidyl)oxy-2-pyridyl]methylthio-1H-benzimidazole (7.48 g) in chloroform (150 ml) was added m-chlorobenzoic acid, and the mixture was stirred at room temperature for 20 minutes.

After cooling the mixture to -20°C, 80% m-chloroperbenzoic acid (4.36 g) was added, and the mixture was stirred for 30 minutes. Then, ammonia gas was passed through, and the resultant precipitation was filtered off. The filtrate was concentrated under reduced pressure, and the residue was subjected to alumina column chromatography and eluted with chloroform containing 1% ethanolic ammonia to give a sulfinyl compound in amorphous powder.

The obtained sulfinyl compound was dissolved in ethanol, and an aqueous solution of 1.9% sodium hydroxide (10 ml) was added thereto. After stirring for 10 minutes, the mixture was concentrated under reduced pressure. Deionized water (100 ml) was added to the residue, then magnesium chloride was added while stirring, and the precipitated crystals were collected by filtration to give 2-[3-methyl-4-(1-benzyl-4-piperidyl)oxy-2-pyridyl]methylsulfinyl-1H-benzimidazole $\frac{1}{2}$ magnesium salt dihydrate (Compound 24).

Elemental analysis for $C_{26}H_{28}N_4O_2S$ $\frac{1}{2}$Mg $2H_2O$			
Calculated Found	C 61.50; C 61.04;	H 6.15; H 5.92;	N 11.03 N 10.70

Examples 3-25

In the same manner as above, the following compounds can be obtained.

(3) 2-[3-methyl-4-(1-benzyl-2-piperidyl)methoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 25), m.p. 82-85°C

(4) 2-[3-methyl-4-(2-(N-methyl-N-(2-thienylmethyl)amino)ethoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 26), m.p. 104-108°C (decomposition)

(5) 2-[3-methyl-4-(2-(N-methyl-N-(2-thienylmethyl)amino)ethoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole $\frac{1}{2}$ magnesium salt dihydrate (Compound 27)

Elemental analysis for $C_{22}H_{24}N_4O_2S_2$ $\frac{1}{2}$Mg $2H_2O$			
Calculated Found	C 54.22; C 54.17;	H 5.58; H 5.22;	N 11.49 N 11.45

(6) 2-[3-methyl-4-(1-benzyl-2-piperidyl)methoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole$\frac{1}{2}$ magnesium salt 5/2 hydrate (Compound 28)

Elemental analysis for $C_{27}H_{30}N_4O_2S$ $\frac{1}{2}$Mg $5/2H_2O$			
Calculated Found	C 61.10; C 61.40;	H 6.45; H 6.13;	N 10.56 N 10.32

(7) 2-[3-methyl-4-(2-(N-methyl-N-(3-thienylmethyl)amino)ethoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 29)

(8) 2-[3-methyl-4-(2-(N-methyl-N-(3-thienylmethyl)amino)ethoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 30)

(9) 2-[3-methyl-4-(2-(N-methyl-N-(3-methyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 31)

(10) 2-[3-methyl-4-(2-(N-methyl-N-(3-methyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 32)

(11) 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 33)

(12) 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]metfiylsulfinyl-1H-benzimidazole (Compound 34)

(13) 2-[3-methyl-4-(2-(N-methyl-N-(5-ethyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]methylthio-1H-benzimidazole (Compound 35)

(14) 2-[3-methyl-4-(2-(N-methyl-N-(5-ethyl-2-thienylmethyl)amino)ethoxy-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 36)

(15) 2-[3-methyl-4-(2-(N-methyl-N-(5-bromo-2-thienylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole (Compound 37)
(16) 2-[3-methyl-4-(2-(N-methyl-N-(5-bromo-2-thienylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 38)
(17) 2-[3-methyl-4-(2-(N-methyl-N-(2-furylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole (Compound 39)
(18) 2-[3-methyl-4-(2-(N-methyl-N-(2-furylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 40)
(19) 2-[3-methyl-4-(2-(N-methyl-N-(3-furylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole (Compound 41)
(20) 2-[3-methyl-4-(2-(N-methyl-N-(3-furylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 42)
(21) 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-furylmethyl)amino)ethoxy)-2-pyrldyl]methylthio-1H-benzimidazole (Compound 43)
(22) 2-[3-methyl-4-(2-(N-methyl-N-(5-methyl-2-furylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 44)
(23) 2-[3-methyl-4-(2-(N-methyl-N-(2-pyridylmethyl)amino)ethoxy)-2-pyridyl]methylthio-1H-benzimidazole (Compound 45)
(24) 2-[3-methyl-4-(2-(N-methyl-N-(2-pyridylmethyl)amino)ethoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole (Compound 46)
(25) 2-[3-methyl-4-(3-methyl-(3-propoxy)-2-pyridyl]methylsulfinyl-1H-benzimidazole sodium salt (Compound 47)

Formulation Examples

Tablets

The tablets containing 20 mg of the active ingredient can be prepared according to the following formulation.

Compound of Example 1	20 mg
Corn starch	15 mg
Lactose	57 mg
Microcrystalline cellulose	25 mg
Magnesium stearate	3 mg
	120 mg

Capsules

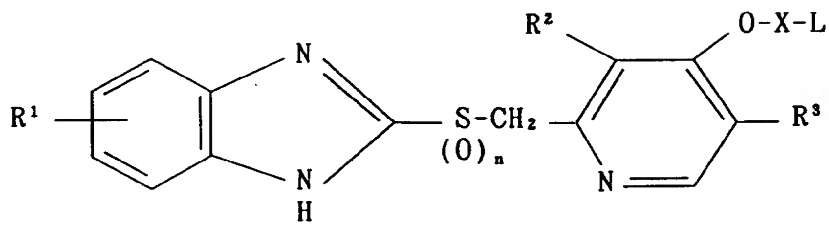
The capsules containing 20 mg of the active ingredient can be prepared according to the following formulation.

Compound of Example 1	20 mg
Corn starch	30 mg
Lactose	63 mg
Hydroxypropylcellulose	6 mg
Magnesium stearate	1 mg
	120 mg

While the present invention has been adequately and sufficiently described by the foregoing specification and examples contained in the specification, it should be understood that the invention is susceptible to various modifications and alternative forms within the spirit and scope of the invention.

Claims

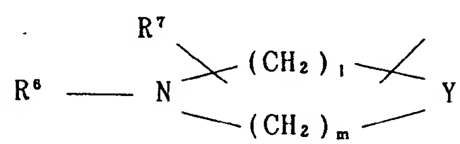
1. An agent for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*, comprising a pyridine compound of the formula



wherein R^1 is hydrogen, halogen, alkyl, alkoxy, alkoxycarbonyl, or haloalkyl, R^2 and R^3 are the same or different and each is hydrogen, halogen or alkyl, n is 0, 1 or 2, X is single bond or alkylene, and L is alkoxy, a group of the formula

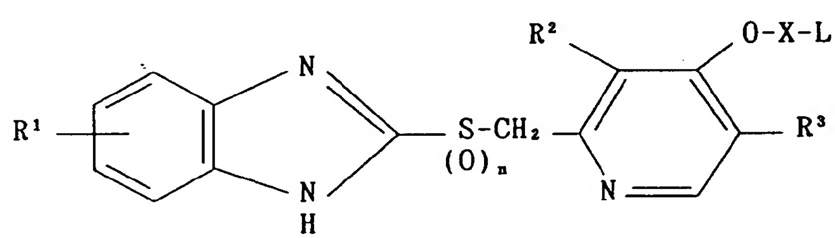
$$-N\begin{matrix} R^4 \\ R^5 \end{matrix}$$

wherein R^4 and R^5 are the same or different, and each is hydrogen, alkyl, acyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, or furylalkyl, thienylalkyl or pyridylalkyl which may be substituted, or R^4 and R^5 together with the adjacent nitrogen atom form a heterocyclic ring which may be condensed, or a group of the formula

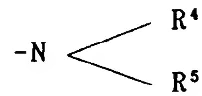


wherein R^6 is hydrogen, alkyl, acyl, phenylalkyl, or substituted phenylalkyl, R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroarylalkyl, or substituted heteroarylalkyl, Y is methylene, oxygen or sulfur, and l and m are the same or different and each is 0, 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

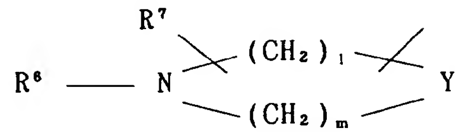
2. An agent for inhibiting recurrence and relapse of ulcer, a suppressant of vomiting, or an agent for the prevention and treatment of non-ulcer dyspepsia, comprising a pyridine compound of the formula



wherein R^1 is hydrogen, halogen, alkyl, alkoxy, alkoxycarbonyl, or haloalkyl, R^2 and R^3 are the same or different and each is hydrogen, halogen or alkyl, n is 0, 1 or 2, X is single bond or alkylene, and L is alkoxy, a group of the formula

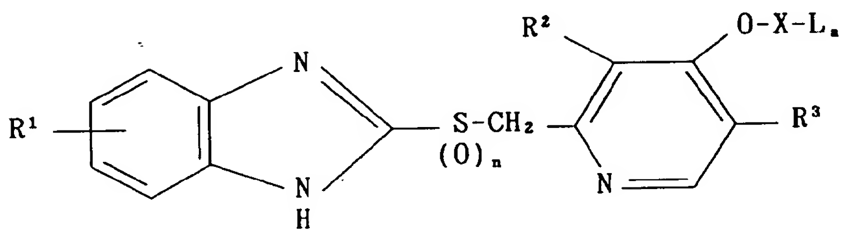


wherein R^4 and R^5 are the same or different, and each is hydrogen, alkyl, acyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, or furylalkyl, thienylalkyl or pyridylalkyl which may be substituted, or R^4 and R^5 together with the adjacent nitrogen atom form a heterocyclic ring which may be condensed, or a group of the formula

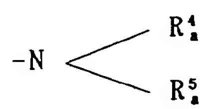


wherein R^6 is hydrogen, alkyl, acyl, phenylalkyl, substituted phenylalkyl, R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroarylalkyl, or substituted heteroarylalkyl, Y is methylene, oxygen or sulfur, and l and m are the same or different and each is 0, 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

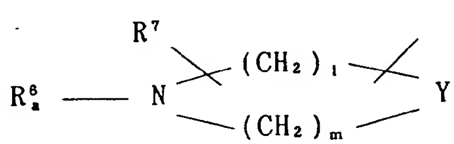
3. A pyridine compound of the formula



wherein R^1 is hydrogen, halogen, alkyl, alkoxy, alkoxycarbonyl, or haloalkyl, R^2 and R^3 are the same or different and each is hydrogen, halogen or alkyl, n is 0, 1 or 2, X is single bond or alkylene, and L_a is a group of the formula



wherein R^4_a is alkyl and R^5_a is furylalkyl, thienylalkyl or pyridylalkyl which may be substituted, or a group of the formula



wherein R^6_a is phenylalkyl or substituted phenylalkyl, R^7 is hydrogen, halogen, alkyl, alkoxy, haloalkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroarylalkyl, or substituted heteroarylalkyl, Y is methylene, oxygen or sulfur, and l and m are the same or different and each is 0, 1, 2 or 3, or a pharmaceutically acceptable salt thereof.

4. An agent for the prevention and treatment of disorders in the digestive tract, comprising the compound of Claim 3.

5. The agent for the prevention and treatment of disorders in the digestive tract, according to Claim 4, wherein the agent for the prevention and treatment is an antiulcer.

6. A method for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter*, comprising administration of the compound of Claim 1 or Claim 3.

7. A method for inhibiting recurrence and relapse of ulcer, or for suppressing vomiting, or for the prevention and treatment of non-ulcer dyspepsia, comprising administration of the compound of Claim 1 or Claim 3.

8. Use of the pyridine compound of Claim 1 or Claim 3, or a pharmaceutically acceptable salt thereof for the production of an agent for the prevention and treatment of various diseases caused by the bacteria belonging to the genus *Helicobacter.*

9. Use of the pyridine compound of Claim 1 or Claim 3, or a pharmaceutically acceptable salt thereof for the production of an agent for inhibiting recurrence and relapse of ulcer, or a suppressant of vomiting, or an agent for the prevention and treatment of non-ulcer dyspepsia.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP91/00037

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl^5 C07D401/12, 401/14, 405/14, 409/14, 413/14, 417/14, A61K31/44, 31/535, 31/54

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
IPC	C07D401/12-401/14, 405/14, 409/14, 413/14, 417/14, A61K31/44, 31/535, 31/54

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JP, A, 59-181277 (Aktiebolaget Hassle), October 15, 1984 (15. 10. 84), Columns 1 to 11 & DE, A, 3404610, FR, A, 2543551	1, 2, 3
X	JP, A, 2-22225 (Eisai Co., Ltd.), January 25, 1990 (25. 01. 90), Column 1	1, 2, 3
X	JP, A, 1-6270 (Eisai Co., Ltd.), January 10, 1989 (10. 01. 89), & EP, A, 268956	1, 2, 3
X	JP, A, 2-22273 (Yoshitomi Pharmaceutical Co., Ltd.), January 25, 1990 (25. 01. 90), Columns 1 to 4 & WO, A, 8900566	1, 2, 3
A	JP, A, 61-85383 (Banyu Pharmaceutical Co., Ltd.), April 30, 1986 (30. 04. 86)	1, 2, 3

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
April 5, 1991 (05. 04. 91)	April 15, 1991 (15. 04. 91)
International Searching Authority	**Signature of Authorized Officer**
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(11) EP 0 587 659 B1

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(54) **PHARMACEUTICAL CARRIER**
PHARMAZEUTISCHER TRÄGER
EXCIPIENTS PHARMACEUTIQUES

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(56) References cited:
EP-A- 0 231 039 **EP-A- 0 415 794**

- **Biotechnology and Applied Biochemistry, Vol. 10, 1988, KARIN LOVGREN et al.: "The requirement of lipids for the formation of immunostimulating complexes (iscoms)", see page 161 - page 172.**
- **Biochimica et Biophysica Acta, Vol. 1062, 1991, GIDEON F.A. KERSTN et al.: "On the structure of immmune-stimulating saponin-lipid complexes (iscoms)" see pp. 165-171**

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EP 0 587 659 B1

Description

The present invention relates to the use of nano particles as pharmaceutical carriers, and pharmaceutical compositions containing said particles.

The use of colloidal particles of micrometer size as pharmaceutical carriers in different forms of administration has been the object of many investigations during the last decades. Lately, one has also succeeded in producing nano particulate carriers and demonstrated that they have large possibilities to facilitate the uptake of incorporated drugs.

In intravenous administration of colloidal particles they will be retrieved in different organs depending on the size and surface characteristics of the particles. Particles having a diameter larger than 7 μm are normally caught by the lung capillaries. Particles of the size 100 nm - 5 μm are effectively eliminated by the reticuloendothelial system (RES), principally by the liver. This is a very fast process which normally gives the particles in the blood a half-life shorter than 1 minute. The rate of elimination can be strongly reduced if the surface of the particles is modified by being coated with substances making it hydrophilic.

Particles being smaller than 100 nm can theoretically, if they are not quickly eliminated by RES, leave the systemic circulation through gaps in the endothelium lining the inside of the blood vessels. Said gaps are of different size in different capillar beds. The endothelium in the pancreas, intestines and kidneys thus has gaps of 50-60 nm while the endothelium of the liver, spleen and bone marrow has gaps of about 100 nm. The blood vessels in certain tumours are also believed to have a more permeable endothelium allowing particles of nano size to pass into the tumour tissue. It has also recently been discovered that nano particles can penetrate the mucous membrane of the intestines, which should facilitate good absorption after oral administration of drugs which are sparingly soluble.

Pharmaceutical carriers in the form of injectable nano particles have therefore been of great interest, especially for the administration of drugs to tumours, and for sustained release of drugs and for the possibility of affecting the distribution in the body of the drug after intravenous injection.

Although many different materials have been investigated with respect to the use as a matrix material for particulate pharmaceutical carriers there are only a few which have turned out to be of use for particles of nanometer size, i.e. certain liposomes, lipoproteins, especially Low Density Lipoproteins (LDL). and a few polymeric material, primarily polyalkylcyanoacrylate.

The use of said known nano particulate carriers is however associated with many problems. Liposomes are quickly eliminated by RES and are in addition fragile which brings about liposome formulations which are instable and hard to handle. LDL is an article in short supply which is extracted from blood. in addition only very hydrophobic drugs can be incorporated without a first transformation into prodrugs. Polymeric pharmaceutical carriers are quickly eliminated by the RES and are in addition obtained in a broad size distribution which makes the control of the release of incorporated drugs more difficult.

Morein et al describe in WO 90103184 an iscom-matrix consisting of a complex between at least one lipid, such a cholesterol, and one or more saponins for use as an immunomodulating agent. This matrix, which has the characteristic iscom structure i.e. an open spherical structure having a diameter of about 40 nm formed from annular sub-units having a diameter of about 12 nm, is said to have an adjuvant effect and is intended for use together with one or more antigens. In the same application it is also demonstrated that the saponins in Quil A, an extract from the bark or Quillaja saponaria molina, can be divided into different substances, inter alia B2, B3 and B4b, some of which show adjuvant effect and others a structure giving effect. Morein et al. in Nature, Vol 308, No 5958, p 457-460 (1984) for the first time describe immunostimulating complexes, which are now commonly named iscoms, which have been formed between antigen determinants having hydrophobic areas and glycosides, such as triterpenesaponins and especially Quil A having an adjuvant effect, and which give an immunogenic effect 10-100 times higher than a normal mixture of antigen and Quil A.

It has now surprisingly turned out to be possible to use a particle of the same type as has previously been used as an adjuvant, as a carrier for the administration of drugs. The drug carrying particle in accordance with the invention does not comprise antigen or antigenic determinants and is therefore immunologically inert.

The term adjuvant refers ideally to a substance which can be used for increasing the immunological response to another substance without initiating an immunological response to itself. In addition in this specification

matrix = carrier	refers to a structure giving complex between one or more saponins and cholesterol, which in addition optionally also contains other lipids, which can be immunologically inert or immunostimulating depending on the saponins which are included, having the form of spherical nano particles formed by annular subunits,
iscom	refers to matrix + antigen, an immunostimulating complex having the same particle structure as the matrix,
delpha	refers to matrix + drug, a drug carrying particle having the same structure as the matrix.

The present invention comprises a drug carrying particle comprising a structure-giving matrix of a complex of a sterol and one or more saponin components as a carrier to which has been connected a pharmaceutically active sub-

stance which particle has an annular basic structure which can form spherical nano particles, especially of size 30-50 nm characterised in that the saponin components have no adjuvant effect.

According to a preferred aspect the matrix also comprises one or more other lipids, especially phospholipids.

The carrier particles preferably have a size of 30-50 nm, especially about 40 nm.

Drug carrier particles according to the invention have the following advantages:

- a narrow particle size distribution, which is of great importance in the administration of a drug in order to obtain a good reproducibility and uniform dosage;
- a sustained duration in the circulation owing to a hydrophilic surface;
- high stability;
- a possibility to bind amphiphilic and lipophilic pharmaceutical substances which are normally very sparingly soluble and hard to formulate.

It has turned out that a sterol, such as cholesterol, is necessary for the desired matrix to be formed. Useful sterols are in this context those who bind to saponins forming the wanted matrix structure, such as precursors and derivatives of cholesterol, as for example β-sitosterol, stigmasterol and thiocholesterol, the last mentioned of which can especially be used for binding a drug by means of the thiol moiety.

The saponins in question for the formation of complex is every structure forming saponin having hydrophobic areas such as those described in R Tschesche and Wulf, Chemie Organischer Naturstoffe, ed. W. Herz, H. Grisebach, G W Kirby, volume 30. (1973). Of special interest are very polar saponins, preferably polar triterpenesaponines such as polar acid bisdesmosides, e g saponin extract from Quillaja bark. Pure saponins without adjuvant effect are especially preferred, such as the substances obtained according to WO 90/03184 from an extract of Quillaja Saponaria Molina having 8-11 carbohydrate groups, i e B4b having a molecular weight of 1862, and optionally B2 having a molecular weight of 1988. The saponin fractions LT 15 and LT 17 have been obtained from the same extract by an alternative method based on a preparative column chromatographic procedure employing similar chromatographic conditions as the thin-layer analytical method described in WO 90/03184.

In addition to the sterol it is of advantage that the matrix comprises one or several other lipids. As example of lipids can be mentioned fats or fatty substances, such as triglycerides or mixed triglycerides containing fatty acids having up to 50 carbon atoms, e g butyric acid, caproic acid, capric acid, caprylic acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid or unsaturated fatty acids having up to 30 carbon atoms such as hexadecenic acid, unsaturated hydroxy fatty acids; glycerol ethers, waxes, i e esters of higher fatty acids and monovalent alcohols; phospholipids such as derivatives of glycerolphosphates such as derivatives of phosphatidic acids i e lecitine, cephaline, inostitolphosphatides, sphingosine derivatives having 14, 15, 16, 17, 18, 19 or 20 carbon atoms; glycolipids, isoprenoids, sulpholipids, carotenoids, steroids, sterols, cholestanol, caprostanol, phytosterols for instance stigmasterol, sitosterol, mycosterols, for instance ergosterol, bile acids for instance cholic acid, deoxycholic acid, kenodeoxycholic acid, litocholic acid, steroid glycosides, esters of vitamin A or mixtures thereof. Especially preferred are phospholipids, such as phosphatidylethanolamin, phosphatidylcholin.

It is of course desirable that the starting compounds used for preparing the carrier particles have a toxicity as low as possible. Owing to its stability the matrix which has been formed, however, normally shows a considerably lower toxicity than the sum of the included components.

As mentioned above the structure of delpha is identical to the structure of the matrix. By means of negatively stained electron microscopy an open spherical structure appears, having a diameter of 30-50 nm, especially 35-42 nm, being made up from more or less annular units having a diameter of 10-12 nm. On the enclosed electron micrographs Figures 1, 3 and 6 show different carrier matrices which can be used in accordance with the invention for the administration of pharmaceutically active substances. Figures 2, 4, 5 and 7 show less well defined complexes and Figure 8 shows a defined CoQ_{10}-delpha. From this can be seen that all carrier matrices as well as the drug carrying particle show the same regular structure within a fairly narrow size interval.

A typical delpha consists of a cholesterol, one or more saponin components, such as B4b or a mixture of B4b and B2, a pharmaceutically active substance and a lipid, normally a phospholipid. Such a typical delpha having a particle size of 30-50 nm has a molecular ratio saponin: cholesterol:phospholipid: drug of 1:(0.1-10):(0-10):(0.1-50), wherein the saponin quotient consists of 10-100 % B4b and the remainder B2 and optionally other saponines. A normal delpha has a molecular composition of 1:1:0.5:0.5, the saponin being B4b.

For the preparation of a matrix or a delpha having annular particles of the size having a diameter of 10-12 nm the proportion between the different components saponin: cholesterol: phospholipid can be changed.

The structure giving matrix used as a carrier, as well as delpha, can be prepared in accordance with WO 90/03184 by solubilisation or transferring into a colloidal form of the sterol in a solvent, addition of the saponin or the saponins and optial additional additives, especially a pharmaceutically active substance, and then the solvent is removed or the concentration is decreases and the complex transferred to a solution in which the components thereof are not soluble, for instance an aqueous solution. This can be done by affinity chromatography, gelfiltration or centrifugation, ultrafiltration,

dialyse, electrophoresis or by evaporation of the solvent or by decreasing the concentration of the solvent by dilution. The matrix and delpha, respectively, are then purified from the excess of sterol and saponins for instance by gelfiltration or centrifugation through a density gradient. As solubilizing agent can be used a detergent, such as a nonionic or ionic, such as cathionic or anionic or zwitterionic detergent, such as Zwittergent or a detergent based on bile acid used in excess. Typical examples are mentioned in WO 90/03184 mentioned above. The solubilizing agent is removed at conditions when the pharmaceutically active substance has sufficiently hydrophobic characteristics for being integrated into the delpha complex as formed. Some surfaceactive substances considerably facilitate the formation of the matrix. They comprise biological membrane lipids having a polar main group and a non-polar aliphatic chain, for instance phosphatidylcholine (negatively charged) and phosphatidylethanolamine (positively charged). The solubilizing agent can also be the solvent per se, such as alcohols, organic solvents or small amphiphatic molecules such as heptane-1,2,3-triol, hexane-1,2,3-triol, acetic acid or trifluoro acetic acid. Preferably ethylalcohol, dioxane, ether, chloroform, acetone, benzen, acetic acid, carbon disulfide, MEGA-10 (N-decanoyl-N-methylglucamine) and β-octylglucoside can be used.

In general it is necessary to remove the solubilizing agent from the matrix, which for instance can be done by dialysis, ultrafiltration, evaporation or column chromatographical technique. In certain cases it can also be possible after binding of the pharmaceutically active substance in question to dilute the obtained drug carrying particles to a concentration giving a physiologically acceptable solution.

The drug carrying particle in accordance with the invention can be prepared by incorporating a pharmaceutically active substance in the carrier matrix by hydrophobic interaction during the formation of the matrix complex as above, but also after the formation of the carrier material. The pharmaceutically active substance can in addition to hydrophobic interaction be linked to the carrier matrix by chemical coupling in a way known per se to a suitable functional group which has been integrated into a previously formed matrix.

As an example of functional groups suited for binding the pharmaceutically active substance can be mentioned -NH_2, -SH, -COOH, -OH. A number of groups and methods of coupling are described in Journal of Immunological Methods, 59 (1983), 129-143, 289-299; in Methods of Enzymology, volume 93, p 280-333; and in Analytical Biochemistry 116, p 402-407 (1981).

Pharmaceutically active substances which can be incorporated into a carrier matrix in accordance with the invention may be of varied composition and size. They are either to be incorporated as solitary units or in combination with other molecules. The binding can occur by means of hydrophobic interaction or through a covalent binding. As an example can be mentioned large glycoproteins having a molecular weight of up to 400 kd and oligopeptides with some few amino acids that can be bound by hydrophobic interaction. Also native proteins, triterpenoids and flavines etc can be incorporated through hydrophobic interaction. Certain substances, for instance a number of proteins, poly- and oligopeptides can be incorporated through hydrophobic interaction after the hydrophobic regions having been exposed by various treatments of a denaturating character. Non-hydrophobic molecules can be incorporated into delpha complexes through covalent bindings to incorporated lipophilic components, for instance phosphatidyl-ethanolamine or covalent bindings to sugar, aldehyde etc.

The invention also refers to a pharmaceutical composition comprising drug carrying particles as above in combination with a pharmacologically acceptable vehicle. Many conventional pharmaceutical vehicles normally being part in different types of drugs can be used. The delpha particles can for instance be suspended in aqueous solutions or be freeze-dried in the formulations. As example of types of drugs containing delpha the following can be mentioned:

* injection fluids, injection and infusion substances and implant tablets for parental administration.
* "solutions", gels, ointments and creams for topical administration.
* capsules, tablets, dragées and mixtures for oral administration.

The concentration of delpha in the different formulations of drugs may vary depending on the included drugs and the way of administration. Normally 1 ml or 1 g of pharmaceutical formulation may contain 0.01 - 100 mg delpha.

The drug carrying particle in accordance with the invention, delpha, can be used in peroral and parenteral administration of pharmaceutical substances. Furthermore, the delpa can be used for topical administration, for instance via the eye, nose and skin, of pharmaceutical substances intended for systemic effect. Also very sparingly soluble pharmaceutical substances can be incorporated into delpha. An example of a substance extremely difficult to dissolve is coenzyme Q_{10}, as well as nifedipine, which today are not available on the market as an injection liquids due to their solubility characteristics. There are other substances difficult to dissolve in the groups of corticosteroids and steroid hormones. Furthermore there are certain cytostatics, for instance ethoposide, that are sparingly soluble.

Delpha can also be used for parenteral administration of drugs with a short biological half-life. These must be administrated by giving repeated injections, as oral administration is impossible due to enzymatic degradation. A sustained release of said drugs from a delpha particle would make possible fewer injections. As examples of pharmaceutically active substances can be mentioned insulin, growth-hormone, calcithonine, GHRH (growth-hormone-releasing hormone).

Another preferred field of use for the drug carrying particles according to the invention is for parenteral target con-

trolled administration of drugs, especially cytostatica.

In the drug carrying particle, delpha, components may be part of several combinations with different molecules and in this connection it has been shown that the components included have been incorporated by tested cells (macrophages and cells from the cell line Wehei 110). With immunofluorescence and electron microscopy it has been possible to follow the complex into the cell, while micells of the corresponding protein have been disintegrated. Consequently this means that the delpha particles are very stable. The uptake and transportation from the injection site is rapid and the components bound to the carrier matrix according to the invention are transported to different organs, such as for instance draining lymphatic organs. After intraperitoneal administration a comparatively large amount of the components are to be found in the spleen. Other organs are the heart, liver, bile, spleen, kidneys, ureter and urine bladder, lungs. A combination of different components in one and the same particle may imply synergism, as different components may have different tasks; one component may for instance target a certain organ or type of cell or for the penetration of mucous and another component may influence the cell. The components in such a complex can be taken up by one and the same cell which is to be influenced.

The carrier matrix according to the invention, as well as a delpha formed in the same way, is characterized in that neither an antibody mediated immunity (AMI) nor a cell mediated immunity (CMI) is developed against the components included therein. Since no immune response is developed against the carrier matrix it can be used as a carrier for various drugs on repeated occasions without immunological reactions preventing for instance a penetration of mucus in local application in for instance the nose, the conjunctive or per os, or prevent adsorption and further distribution of the carrier or delpha and drugs incorporated therein in the organism in parenteral application. Immunological reactions causing secondary effects can thus be avoided.

For the preparation of a pharmaceutical composition a kit can be provided, comprising separate packages of particles of a structure-giving matrix according to the invention, optionally in combination with a surface-active substance, and a pharmacologically acceptable vehicle.

The invention is furthermore illustrated by the following examples of the preparation and use of a structure giving carrier matrix and drug carrying particles under reference to the enclosed drawings.

Figure 1 shows in a magnification of 200,000 an electon micrograph of a carrier matrix of the invention as prepared in example 2 from Quil A, cholesterol and phosphatidylethanolamine;

Figure 2-4 show in a magnification of about 75,000 electron micrographs of three other carrier matrices prepared in accordance with example 3 from Quil A and three different sterols, that is stigmasterol, β-sitosterol and lanosterol;

Figure 5-7 show in a magnification of about 75,000 electron micrographs of three other carrier matrices as prepared in example 4 from Quil A, phosphatidylcholine and one of stigmasterol, β-sitosterol and lanosterol respectively;

Figure 8 shows in a magnification of about 75,000 an electron micrograph of delpha particles containing CoQ_{10}, prepared in accordance with example 5;

Figure 9 shows in a magnification of about 75,000 an electron micrograph of delpha particles containing amfotericin B, which have been prepared in accordance with example 6 b);

Figure 10 refers to the absorbance and counts respectively of different fractions obtained in analysing the delpha particles displayed i figure 9;

Figure 11 shows in a magnification of about 75,000 an electron micrograph of delpha particles containing amfotericin B, which have been prepared in accordance with example 6 d); and

Figure 12 refers to the absorbance and counts respectively of different fractions obtained in analysing the delpha particles displayed in figure 11.

In the following examples, No. 1-4 refer to the preparation of carrier particles to which a desired drug can be covalently coupled; No. 5-6 refer to a direct preparation of delpha particles, that is particles wherein a drug has been incorporated into the matrix by hydrophobic interaction; and No. 7-8 refer to the preparation of delpha particles wherein the drug has been covalently coupled to the carrier matrix.

Example 1 Delpha carrier

A carrier for non-hydrophobic pharmaceuticals is prepared as follows. 1000 μl lipid-mix consisting of 10.0 mg cholesterol (+ traces of ^{3}H-cholesterol), 10.0 mg phosphatidylethanolamine and 200 mg MEGA-10 (N-decanoyl-N-methylamine) in H_2O are mixed with 500 mg LT15 (a saponin fraction obtained from Karlshamns Lipidteknik AB, Stockholm, Sweden) dissolved in H_2O (10 % w/w) and the volume is adjusted to 5-10 ml with PBS (0.02 M phosphate buffered saline, 150 mM NaCl, pH 7.4). The mixture is incubated on a shaker for 4-24 hrs before it is dialysed against 5x5 l PBS (ambient temperature for 24-48 hrs., thereafter at +4°C).

The formed carrier complexes are purified from excess material on a sucrose gradient, 10-50 % w/w, 18 hrs.,

400,000 rpm (rotor TST 41.14), 10°C. The gradient is emptied from below in 17 fractions which are analysed as to carrier particles (^{3}H-cholesterol and electron microscopy, EM) according to the table 1 below. Fractions containing carrier particles are pooled and the exact amount of the included components (cholesterol, phosphatidylethanolamine and saponin) are determined. The carrier particles can for exemple be concentrated by pelleting (18 hrs., 40,000 rpm (TST 41.14), 10°C). A pelleted carrier is dissolved to a requested concentration of for exemple 10 mg/ml, in a suitable buffer and is stored at a temperature of +4°C (1 month) or -70°C (long-term storage) until use.

Table 1

Fraction No.	Cholesterol (cpm)	Particles (EM)
1	30	-
2	20	-
3	27	-
4	41	-
5	246	+
6	11807	+++++
7	6802	++++
8	2577	+++
9	968	++
10	570	+
11	471	(+)
12	329	-
13	275	-
14	197	-
15	139	-
16	315	-
17	576	-

The same effect is obtained if LT 15 is replaced by a mixture of LT 15 and LT 17.

Example 2 Delpha carriers

A carrier for non-hydrophobic pharmaceuticals is prepared as follows. 1000 µl lipid-mix, consisting of 10.0 mg cholesterol (+ traces of ^{3}H-cholesterol), 10.0 mg phosphatidylethanolamine and 200 mg MEGA-10 (N-decanoyl-N-methylglucamine) in H_2O are mixed with 500 mg Quil A (Spikosid, from Iscotec, Luleå) dissolved in H_2O (10 % w/w), the volume is adjusted to 5-10 ml with PBS (0.02M phosphate buffered saline, 150 mM NaCl, pH 7,4). The mixture is incubated in shaking for 4-24 hrs before it is dialysed against 5 X 5 l PBS (ambient temperature for 24-48 hrs, thereafter +4°C). The carrier particles can be concentrated, analysed and stored according to example 1. The result of the analyses is given in Table 2 below.

Table 2

Fraction No.	CPM (3H-cholesterol)	EM (matrix structure)
1	59	
2	54	
3	71	
4	2562	++
5	22801	+++
6	44101	+++
7	17900	+++
8	5717	+++
9	2394	++
10	1471	+
11	970	
12	732	
13	513	
14	676	
15	408	
16	353	
17	690	

Figure 1 shows in a magnification of 200 000 times the carrier matrix of fraction 5, viz. the spherical association complexes of a size of 30-50 nm in diameter, formed from an annular basic structure having a diameter of approximately 10 nm.

The same effect is achieved if instead of Quil A is used 250 mg of each of B2 and B4b, or 500 mg pure B4b.

Example 3 Delpha carriers

A carrier matrix for non-hydrophobic drugs is manufactured as in example 2 by mixing 100 µl of a solution consisting of 1.0 mg stigmasterol and 20 mg MEGA-10 in H_2O with 5.0 mg Quil A.

The mixture is incubated on a shaker for 4-24 hrs before it is dialysed against PBS (ambient temperature for 24-48 hrs, thereafter +4°C). The EM verifies that carrier complexes have been formed. Formed complexes are purified on a sucrose gradient 10-50% w/w for 18 hrs at 40 000 rpm (rotor TST 41,14) at 10°C or by sedimentation through 20% w/w sucrose for 18 hrs at 40.000 rpm (rotor TST 41,14) at 10°C. Sedimented complexes are dissolved in PSB. Figure 2 shows in a magnification of 75.000 the obtained basic structure, here as partially associated.

If stigmasterol in the example above is replaced by β-sitosterol monomer carrier particles of an annular basic structure (10-12 nm) is obtained, as is shown in Figure 3. If stigmasterol instead is replaced by lanosterol the basic structure is obtained in another associated form according to Figure 4.

If Quil A in this example is replaced by LT 15 or a mixture of LT 15 and LT 17 similar structures are obtained.

Example 4 Delpha carriers

A carrier matrix for non-hydrophobic drugs prepared is in accordance with example 2 from 100 µl of a solution consisting of 1.0 mg stigmasterol, 1.0 mg phosphatidylcholine and 20 mg MEGA-10 in H_20 mixed with 5.0 mg Quil A. The mixture is incubated in a shaker for 4-24 hrs before being dialysed against 5 x 51 PBS (ambient temperature 24-48 hrs, then +4°C). The fact that carrier complexes are formed is verified by EM. Formed complexes are purified on a sucrose gradient 10-20% w/w for 18 hrs at 40,000 rpm (rotor TST 41,14) at 10°C or through/by sedimentation through 20% w/w sucrose for 18 hrs at 40.000 rpm (rotor TST 41,14) at 10°C. Sedimented complexes are dissolved in PBS. Figure 5 shows in a magnification of 75,000 times an electromicrograph of the obtained honeycomb structure.

If, on the other hand, stigmasterol in the above example is replaced by β-sitosterol spherical carrier particles in accordance with Figure 6 are obtained with a structure similar to the one shown in Figure 1. If stigmasterol instead is replaced by lanosterol the main part of the material is precipitated, see Figure 7.

These examples show that from the tested sterols stigmasterol presented the "best" preparation, that is a transparent solution without precipitation in the absence of phospholipid. The lanosterol and the β-sitosterol brought about a lesser precipitation in addition to the complexes shown on the EM photograph. When phospholipid was added the solution with lanosterol and stigmasterol, respectively, became opalescent, which indicates that a great part of the material did not form any complex with Quil A. β-sitosterol on the other hand formed a well-defined matrix with Quil A and phospholipid.

Example 5 CoQ_{10} -delpha

2 mg CoQ_{10} are dissolved in about 25 μl chloroform and mixed with a 400 μl lipid-mix, consisting of 4.0 mg cholesterol (+ traces of ^{3}H-cholesterol), 4.0 mg phosphatidylcholine and 80 mg MEGA-10 in H_20. The chloroform is evaporated by a gentle nitrogen bubbling while vigorous stirring of the mixture. The temperature is kept at 25-35°C. When the chloroform has been removed 10 mg Quil A (Spikosid) dissolved in H_2O (10% w/w) is added, the volume is adjusted to 2 ml with PBS [phosphatbuffered (0.02M), 150mM NaCl, pH 8.4}. The mixture is incubated in shaking for 2-4 hrs (in darkness), before being dialysed against 3 X 5 l PBS (in darkness, ambient temperature).

The formed CoQ_{10}-carrying particles are purified from excess material on a sucrose gradient, 10-50% w/w, 18 hrs, 40.000 rpm TST 41,14), 10°C. The gradient is emptied from below in 17 fractions which is each analysed as to the CoQ_{10} (A330) and delpha particles (^{3}H-cholesterol and electron microscopy). Fractions containing CoQ_{10}-delpha are pooled and the exact concentration of CoQ_{10} is determined. 3H-cholesterol is determined by taking 50 μl samples from each fraction in the gradient, mixing with 4 ml scintillation fluid (optiphase Hisafe II, Pharmacia-LKB) and counting for 60 seconds in a β-counter (Rackbeta, LKB). The result is shown in Table 3 below.

Table 3

Fract. No.	CPM (3H-cholesterol	A330 (CoQ_{10})	EM (matrix structure)
1	22	0.055	-
2	23	0.056	-
3	32	0.053	-
4	30	0.081	-
5	25	0.080	-
6	1410	0.149	+
7	12120	0.653	+++
8	9624	0.397	+++
9	3600	0.167	++
10	1513	0.124	+
11	1578	0.289	+
12	1023	0.382	(+)
13	507	0.357	-
14	408	0.213	-
15	437	0.384	-
16	275	0.499	-
17	294	1.225	-

Figure 8 shows in a magnification of 1:75,000 an electron migrograph of the delpha structure obtained in fraction 7, 30-50 nm, similar to the photograph in Figure 1.

The same result is obtained if instead of Quil A 5 mg of each of B2 and B4b are used.

Example 6 Amfotericin B delpha

In order to prepare amfotericin B delpha particles 1 mg amfotericin B was dissolved in 75 µl DMSO and mixed with

a) 2 mg of each of cholesterol and phosphatidyl choline and mixed with 10 mg B4b (LT 15);
b) 3 mg of each of cholesterol and phophatidyl choline and mixed with 15 mg B4b (LT 15);
c) 2 mg of each of cholesterol and phosphatidyl choline and mixed with 8 mg B4b (LT 15) and 2 mg B2 (LT 17); or
d) 3 mg of each of cholesterol and phosphatidyl choline and mixed with 12 mg B4b (LT 15) and 3 mg B2 (LT 17);

in a volume of 1 ml PBS. The complexes were made and analyzed as described in example 1.

The fractions obtained form sucrose density gradient centrifugation were analyzed for cholesterol (cpm), absorbance at 405 nm (amphotericin B) and structure (EM) and showed that amphotericin B efficiently incorporated into delpha particles. The use of ony LT 15 and amfotericin B produces a somewhat aggregated delpha, an addition of LT 17 helped to give non-aggregated particles.

Figure 9 shows an electron micrograph of amotericin B delpha particles prepared according to method b) above in a magnification of about 75,000;

Figure 10 shows a graph of the absorbance and counts respectively obtained from the analysis of the different fractions obtained from the amfotericin B delpha particles prepared according to said method b);

Figure 11 shows an electron micrograph of amfotericin B delpha particles prepared according to method d) above in a magnification of about 75,000;

Figure 12 shows a graph of the absorbance and count respectively obtained from the analysis of the different fractions obtained from the amfoteracin B delpha particles prepared according to said method d).

A larger proportion of LT 17 will give an increased amount of sub units (10-12 nm), which on the graph in figure 12 can be seen as a second peak.

Example 7 LHRH-delpha

LHRH (luteinizing hormone releasing hormone) is conjugated to the carrier matrix in accordance with the principles for conjugation via cysteine by means of maleidohexanoylN-hydroxysuccinimidester (MHS), described by Lee et al , Molecular Immunology, Vol. 17, pages 749-756 (1980).

The peptide is reduced according to the following. 1 mg peptide is dissolved in 400 µl 0.1 M sodiumphosphate buffer pH 8.0. A 250 x molar excess of dithiotreitol (DTT) is added and the mixture is incubated at ambient temperature for 30-60 minutes. The peptide is separated from DTT by gelfiltration on Sephadex G-10 (Pharmacia, Uppsala) equilibrated with deaired N_2saturated 0.1 M sodiumphosphate buffer pH 6.66, containing 0.1 M EDTA.

The carrier matrix according to example 2 is MHS modified as follows: 2.0 mg carrier in 450 µl 0.1 M sodiumphosphate buffer, pH 6.66, is mixed with 10-100 x molar excess of MHS (in 50 µl DMSO) to phosphatidylethanolamine in the matrix. The reaction mixture is stirred gently at ambient temperature for 1 hour. Excess of MHS and other reaction products are removed through gelfiltration at Sephadex G-25 (Pharmacia, Uppsala) equilibrated with deaired N_2saturated 0.1 M sodiumphosphate buffer pH 6,66, containing 0,1 M EDTA. The solution with reduced peptide is mixed with MHS activated carrier in a 5 x molar excess ratio of peptides to phosphatdylethanolamine. The conjugation is allowed to continue during stirring for 18-24 hours.

LHRH-delpha is purified from excess material on a sucrose gradient, 10-50% w/w, 18 hrs, 40.000 rpm (TST 41.14), 10°C. The gradient is emptied from below in 17 fractions which each is analysed as to LHRH and delpha particles (^{3}H-cholesterol and electron microscopy). Fractions containing LHRH-delpha particles are pooled and the concentration is determined.

Example 8 Biotin-delpha

1 mg (2.0 mg/ml) carrier (made according to example 2) in 0.1 M carbonate buffer, pH 8.8, is mixed with N-hydroxysuccinimidebiotin (10 mg/ml in DMS0) in an excess of 10 X 1 in relation to phosphatidylethanolamine. The mixture is incubated for 15 minutes at ambient temperature. The biotin-delpha-particles are purified from surplus material on a sucrose gradient, 10-50% w/w, 18 hrs, 40,000 rpm (TST 41,14), 10°C. The gradient is emptied from below in 17 fractions which each is analysed as to LHRH and delpha particles (^{3}H-cholesterol and electronmicroscopy), see Table 4 below, and biotin. Fractions containing biotin-delpha particles are pooled and the quantity is determined.

Table 4

Fract. No.	CPM (3H-cholesterol)	EM (matrix structure)
1	45	-
2	22	-
3	41	-
4	24	-
5	1314	+
6	14993	++
7	26315	+++
8	8239	++
9	3644	++
10	1704	+
11	1024	
12	673	
13	523	
14	321	
15	230	
16	170	
17	154	

A pool consisting of the fractions 5-10 is analyzed for biotin in an ELISA.

Coat: mouse anti-biotin (monoclonal) 10 g/ml in a 50 mM carbonate buffer, pH 9.6, 4°C over night.
Dilution tests (pool and non-biotinylated matrix):
1/50, 1/150, 1/450 etc in PBS Tween (0.05%), 1 hr, ambient temperature, on a shaker.
Conjugate: avidine-HRP (horse-radish peroxidase) 1/2000 in PBS Tween (0,05%), 1 h, ambient temperature, on a shaker.
Development: TMB (tetramethyl benzidine) 0.10 mg/ml and H_2O_2 (0.006%) in 0.1 M acetate, pH 6.0.

Table 5

Dilution test	ABS (pool)	ABS (control matrix)
1/50	1.997	0.097
1/150	2.107	0.078
1/450	1.874	0.106
1/1350	1.201	0.099
1/4050	1.816	0.100
1/12150	0.206	0.089
1/36450	0.096	0.090
1/109350	0.103	0.115

The following test shows the distribution of drug in the body after administration by means of a delpha according to

the invention.

Biological tests to show that the carrier is immunologically inert

LT 15

LT 15 is an adjuvant depleted fraction of Quil A which has been obtained from Karlshamns Lipidteknik AB.

A conventional saponin adjuvant, like Quil A, potentiates the immune response to an antigen when mixed with the antigen prior to e.g. subcutaneous injection. To confirm that LT 15 (which is very similar to the B4b preparation) is depleted of adjuvant active saponins the following test for adjuvant activity was performed in mice.

3 groups of 5 mice were immunized with 1 μ g of protein micelles made from influensa virus glycoproteins (Lövgren et al 1987) plus:

a) 10 μ g LT 15
b) 10 μ g Quil A
c) saline

Two weeks after immunization the mice were bled and the serum was assayed for antibodies to the viral proteins (standard Elisa technique employing microtine plates coated with the antigen and a commercial enzyme-conjugated rabbit anti-mouse preparation for detection of mouse immunoglobulins). The result shown in table 6 below demonstrates that LT 15 as well as plain saline did not potentiate the antibody response to the protein micelles in contrast to the non-depleted Quil A preparation.

Table 6

Group	Amount of antibody (arbitrary unit)
a)	714+-397
b)	1055+-347
c)	800+-367

Different biotin-carriers

The administration of biotin to mouse using different carriers. In order to verify that the carrier matrix is immunologically inert when used as a drug carrier a comparative test was made with biotin administered as biotin-delpha and with immunologically active carriers. Mice were injected subcutaneously with biotin carried by immunologically active carriers - iscom and micelle respectively - containing surface proteins from an influensa virus. After an immunization with 3 μg carrier-biotin all mice had high (iscom) or medium high (micelle) serum titres against biotin. Eight weeks later the mice were given a "booster-dose" with biotin-delpha-particles. Two weeks later serum samples were taken and the amount of antibodies against biotin before and after the administration of the biotin-delpha was compared. A control group of animals was injected with biotin-delpha on both occasions. As appears from Table 7, the administration of biotin-delpha had no effect on the antibody response against biotin not even in those cases when the animals had been primarily immunized against biotin linked to an immunologically active carrier. After a booster with an active carrier the serum titres against biotin were increased 5-10 times (not shown in Table 7).

Table 7

Primary administration		Secondary administration	
biotin-formulation	antibody response against biotin	biotin-formulation	antibody response against biotin
biotin-iscom (33 mice)	2999±467 (1824 - 3781)	biotin-delpha (11 mice)	3101±317 (2301 -3476)
biotin-micelle (33 mice)	973±470 (291±1971)	biotin-delpha (11 mice)	850-486 (398 -1978)
biotin-delpha (34 mice)	59±13 (42-89)	biotin-delpha (11 mice)	49±5 (42-57)

Autoradiography of CoQ_{10}-delpha in mouse

Delpha-particles were prepared by 1 mg CoQ_{10}, 2 mg ^{3}H-cholesterol, 2 mg phosphatidylcholin, 10 mg MEGA-10 and 10 mg LT 15 in a volume of 1 ml H_2O according to example 5. The fractions 5-7 were pooled and the content of cholesterol was determined by means of the ^{3}H-activity to be 0.73 mg cholesterol/ml. The content of CoQ_{10} was estimated to $\leq$ 0.1 mg/ml.

4 female mice were injected subcutaneously in the neck with 0.4 ml of the mixture above. The mice were sacrified and sectioned for autoradiography after 15 min, 2 h, 6 h and 24 h.

After 24 h particles were still present at the site of injection, which indicates that the cholesterol is linked to the particles. Compared with administration of free cholesterol high levels of cholesterol were found in the liver and in the blood; still more in the lungs; and still more in the spleen, bone marrow and local lymphatic organs. It was observed that the level in the blood increased continuously up to 24 h.

From this can be concluded that the cholesterol mainly is particle-bonded; if pure cholesterol is injected there will be a concentration of cholesterol in the adrenal cortex.

Administration of CoQ_{10} to mouse

The length of the isoprene chain in the Coenzyme Q (CoQ) varies in different animal species. CoQ_9 thus contains 9 isoprene units in the chain and CoQ_{10} contains 10 units. Man only produces CoQ_{10} whereas the rat and mouse produce about 95% CoQ_9 and 5% of CoQ_{10}. Due to the low endogene concentration of CoQ_{10} mouse was chosen as for the experiment in the following test:

15 NMRI mice (females) 19.20g $\pm$ 0.90 g were injected subcutaneously with 14.6 μg CoQ_{10}-delpha (0.8 mg/kg) made with B2 + B4b instead of Quil A according to example 5, i e with 0.2 ml of a formulation containing 73 μg/ml CoQ_{10}. At T = 0, 0.5, 1, 3, 5 and 8 hours blood samples were taken and at T = 0, 0.5, 3 and 8 hours organs were also removed (heart, liver, kidneys and spleen). To measure the endogene level a control group of 6 (mice) were injected with empty delpha complexes, i e only carriers in a corresponding amount. Blood samples and organs were taken from this control group at T = 0.5 and 7 hours. As a comparison serum and organs were taken also from 3 non treated mice. The blood was centrifuged and plasma and organs were kept at a temperature of -20°C until analysed. The chemical analyses of CoQ_{10} were carried out with liquid chromatography in accordance with a method described by P-O Englund in J. Chromatogr. 425 (1988), 87-97. The organ samples were homogenised with a Potter-S homogenisator in 10 volumes 1-propane containing an intern standard. The liquid phase was injected into the liquid chromatograph. The chemical analyses showed an increase of the CoQ_{10} content in serum and heart, see table 8. To analyse cholesterol a sample, 1 ml, from the liquid phase is mixed with 8 ml scintillation fluid (Orphphase Hisafe II, Pharmacia LKB) and is counted for 2000 seconds in a β-counter (Rackbeta, LKB). In measuring the radioactivity in the organ samples (3H-cholesterol) a distinct radioactivity was registered only in liver samples.

The following can be concluded from the experiment:

* since the CoQ_{10} part is continuously increased in serum for 8 hours, and probably longer, the delpha complexes have not immediately been eliminated by RES
* the delpha-complex is supposed to have delivered CoQ_{10} to the heart as CoQ_{10} in the heart tends to increase without a corresponding increase of the cholesterol of the complexes being found
* the delpha complexes and/or included cholesterol are likely to be eliminated via the liver which demonstrated the highest degree of radioactivity.

Table 8

Mouse No	Time h	Spleen μg/g	Kidney μg/g	Liver μg/g	Heart μg/g	Serum μg/ml
1 (contr.)	0.5	6.770	11.500	3.050	21.000	0.034
2 (contr.)	0.5	7.100	10.900	2.610	40.800	0.054
3 (contr.)	0.5	6.820	9.760	3.050	21.300	0.031
4 (contr.)	7.0	6.620	11.800	5.160	11.200	0.041
5 (contr.)	7.0	7.040	13.500	2.790	11.400	0.033
6 (contr.)	7.0	8.020	11.100	2.410	10.100	0.015
7 non treated	-	7.970	10.500	3.830	47.400	0.045
8 non treated	-	7.270	11.400	2.780	10.800	0.022
9 non treated	-	7.250	10.600	3.000	44.700	0.020
10	0.5	7.300	11.500	3.240	12.300	
11	0.5	8.270	12.300	3.440	45.100	0.019
12	0.5	6.560	10.500	2.730	11.800	0.030
13	1.0	7.880	10.600	3.360	11.300	0.048
14	1.0	7.300	11.200	3.110	9.520	0.060
15	1.0	7.350	10.700	3.850	40.200	0.019
16	3.0	8.130	10.800	2.900	47.600	0.195
17	3.0	8.340	11.000	2.870	45.400	0.184
18	3.0	7.060	11.300	3.150	37.800	0.131
19	5.0	8.200	11.100	3.070	49.900	
20	5.0	7.240	11.100	3.950	46.700	0.186
21	5.0	7.140	9.950	3.740	41.300	0.247
22	8.0	8.090	11.600	4.020	40.600	0.206
23	8.0	8.770	11.800	3.380	44.600	0.266
24	8.0	7.120	11.800	2.720	47.800	0.203

Claims

1. Drug carrying particle comprising a structure-giving matrix of a complex of a sterol and one or more saponin components as a carrier to which has been connected a pharmaceutically active substance which particle has an annular basic structure which can form spherical nano particles, especially of size 30-50 nm characterised in that the saponin components have no adjuvant effect.

2. Drug carrying particle according to claim 1, characterised in that the matrix also comprises one or more other lipids, especially phospholipids.

3. Drug carrying particle according to claim 1 or 2, characterised in that the spherical particle has a size of 35-42 nm.

4. Drug carrying particle according to claim 3, characterised in that the spherical particle has a size of about 40 nm.

5. Drug carrying particle according to any preceding claim characterised in that the sterol is cholesterol.

6. Drug carrying particle according to any preceding claim characterised in that the saponin component is one or more of the saponins B4b, B2, LT15 or LT17.

7. Drug carrying particle according to any of claims 1-6, characterised in that the matrix is formed from cholesterol and the saponin B4b or LT 15, optionally in combination with the saponin B2 or LT17, and in addition comprises a phospholipid.

8. Drug carrying particle according to any of claims 2-7, characterised in that the phospholipid is phosphatidylethanolamine or phosphatidylcholine.

9. Drug carrying particle according to any of claims 1-8, characterised in that the pharmaceutically active substance has been connected to the matrix by covalent or hydrophobic bonds.

10. Drug carrying particle according to any of claims 1-9, characterised in that the pharmaceutically active substance is CoQ_{10}.

11. Drug carrying particle according to any of claims 1-9, characterised in that the pharmaceutically active substance is amfotericin B.

12. A pharmaceutical composition comprising drug carrying particles according to any of claims 1-11 in combination with a pharmacologically acceptable vehicle.

13. A pharmaceutical composition according to claim 12, adapted for oral administration.

14. A pharmaceutical composition according to claim 12, adapted for parenteral administration.

15. A pharmaceutical composition according to claim 12, adapted for topical administration.

16. Drug carrying particle according to any of claims 1-11, for use in therapy.

Patentansprüche

1. Arzneimitteltragendes Teilchen, umfassend eine strukturgebende Matrix aus einem Komplex aus einem Sterol und einer oder mehreren Saponinkomponenten als Träger, mit dem eine pharmazeutisch aktive Substanz verbunden ist, wobei das Teilchen eine ringförmige Basisstruktur besitzt, die sphärische Nanoteilchen insbesondere mit einer Größe von 30 bis 50 nm bilden kann, dadurch gekennzeichnet, daß die Saponinkomponenten keine Adjuvanswirkung besitzen.

2. Arzneimitteltragendes Teilchen nach Anspruch 1, dadurch gekennzeichnet, daß die Matrix auch ein oder mehrere andere Lipide, insbesondere Phospholipide, umfaßt.

3. Arzneimitteltragendes Teilchen nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß das sphärische Teilchen eine Größe von 35 bis 42 nm besitzt.

4. Arzneimitteltragendes Teilchen nach Anspruch 3, dadurch gekennzeichnet, daß das sphärische Teilchen eine Größe von etwa 40 nm besitzt.

5. Arzneimitteltragendes Teilchen nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß das Sterol Cholesterin ist.

6. Arzneimitteltragendes Teilchen nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß die Saponinkomponente ein oder mehrere der Saponine B4b, B2, LT15 oder LT17 ist.

7. Arzneimitteltragendes Teilchen nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß die Matrix gebildet ist aus Cholesterin und dem Saponin B4b oder LT15, gegebenenfalls in Kombination mit Saponin B2 oder LT17 und zusätzlich ein Phospholipid umfaßt.

8. Arzneimitteltragendes Teilchen nach einem der Ansprüche 2 bis 7, dadurch gekennzeichnet, daß das Phospholipid Phosphatidylethanolamin oder Phosphatidylcholin ist.

9. Arzneimitteltragendes Teilchen nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz mit der Matrix durch kovalente oder hydrophobe Bindungen verbunden ist.

10. Arzneimitteltragendes Teilchen nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz CoQ_{10} ist.

11. Arzneimitteltragendes Teilchen nach einem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz Amfotericin B ist.

12. Pharmazeutisches Mittel umfassend arzneimitteltragende Teilchen nach einem der Ansprüche 1 bis 11 in Kombination mit einem pharmakologisch annehmbaren Hilfsmittel.

13. Pharmazeutisches Mittel nach Anspruch 12, adaptiert für orale Verabreichung.

14. Pharmazeutisches Mittel nach Anspruch 12, adaptiert für parenterale Verabreichung.

15. Pharmazeutisches Mittel nach Anspruch 12, adaptiert für topische Verabreichung.

16. Arzneimittelhaltiges Teilchen nach einem der Ansprüche 1 bis 11 zur Verwendung bei der Therapie.

Revendications

1. Particule supportant un médicament comprenant une matrice structurante d'un complexe d'un stérol et d'un ou plusieurs composant(s) saponine(s) en tant que support à laquelle a été fixée une substance pharmaceutiquement active, ladite particule possédant une structure de base annulaire qui peut former des nanoparticules sphériques, particulièrement de dimension 30-50 nm, caractérisée en ce que les composants saponines n'ont aucun effet adjuvant.

2. Particule supportant un médicament selon la revendication 1, caractérisée en ce que la matrice comprend également un ou plusieurs autres lipides, particulièrement des phospholipides.

3. Particule supportant un médicament selon la revendication 1 ou 2, caractérisée en ce que la particule sphérique a une dimension de 35-42 nm.

4. Particule supportant un médicament selon la revendication 3, caractérisée en ce que la particule sphérique a une dimension d'environ 40 nm.

5. Particule supportant un médicament selon l'une quelconque des revendications précédentes caractérisée en ce que le stérol est le cholestérol.

6. Particule supportant un médicament selon l'une quelconque des revendications précédentes caractérisée en ce que le composant saponine est au moins une des saponines B4b, B2, LT15 ou LT17.

7. Particule supportant un médicament selon l'une quelconque des revendications 1-6, caractérisée en ce que la matrice est formée à partir de cholestérol et de la saponine B4b ou LT15, éventuellement en combinaison avec la saponine B2 ou LT17, et comprend en outre un phospholipide.

8. Particule supportant un médicament selon l'une quelconque des revendications 2-7, caractérisée en ce que le phospholipide est la phosphatidyléthanolamine ou la phosphatidylcholine.

9. Particule supportant un médicament selon l'une quelconque des revendications 1-8, caractérisée en ce que la substance pharmaceutiquement active a été fixée à la matrice par des liaisons covalentes ou hydrophobes.

10. Particule supportant un médicament selon l'une quelconque des revendications 1-9, caractérisée en ce que la substance pharmaceutiquement active est CoQ_{10}.

11. Particule supportant un médicament selon l'une quelconque des revendications 1-9, caractérisée en ce que la substance pharmaceutiquement active est l'amphotéricine B.

12. Composition pharmaceutique comprenant des particules supportant un médicament selon l'une quelconque des revendications 1-11 en combinaison avec un véhicule pharmacologiquement acceptable.

13. Composition pharmaceutique selon la revendication 12, adaptée pour une administration orale.

14. Composition pharmaceutique selon la revendication 12, adaptée pour une administration parentérale.

15. Composition pharmaceutique selon la revendication 12, adaptée pour une administration topique.

16. Particule supportant un médicament selon l'une quelconque des revendications 1-11, pour une utilisation en thérapie.

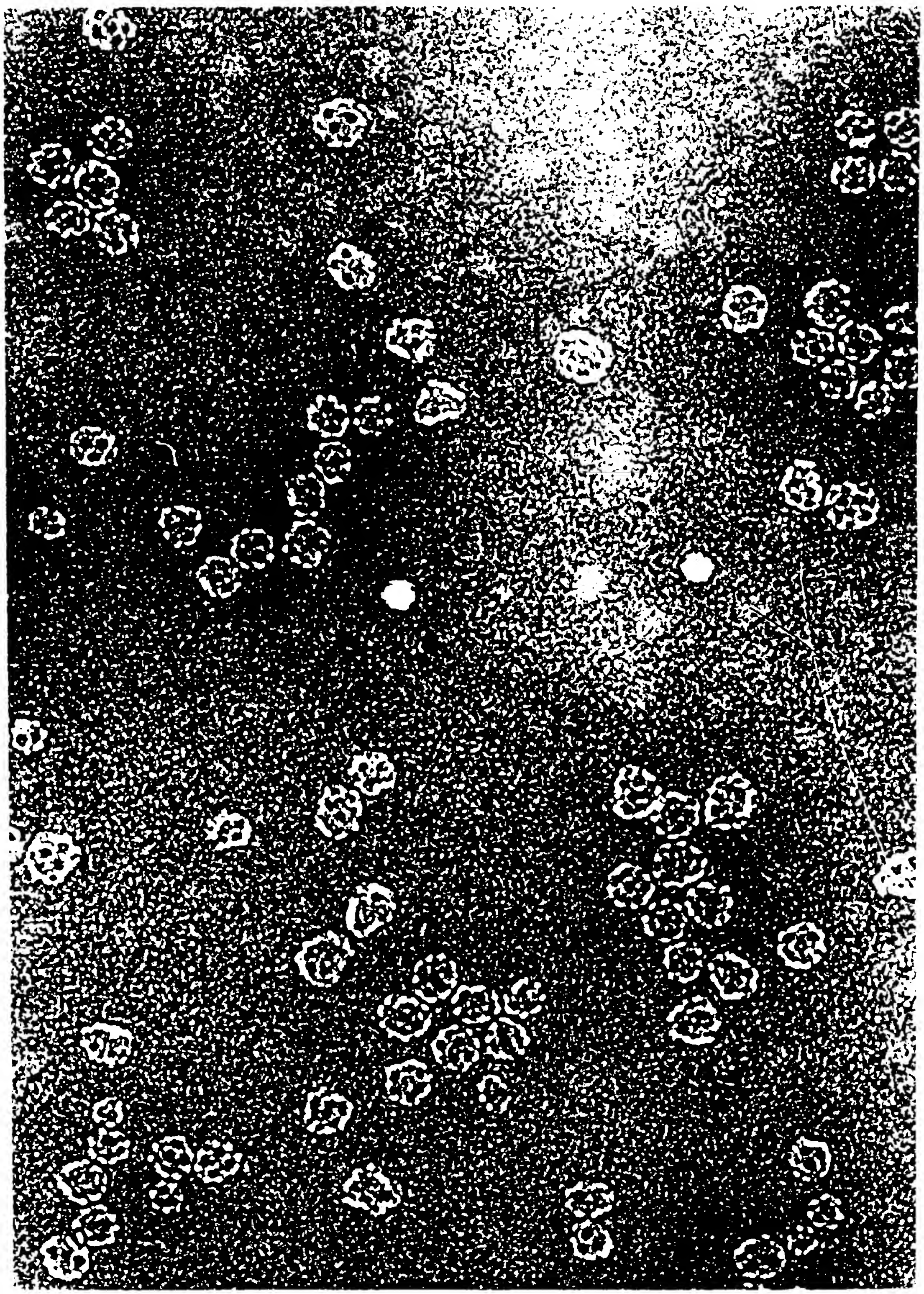


Fig. 1

Fig. 2

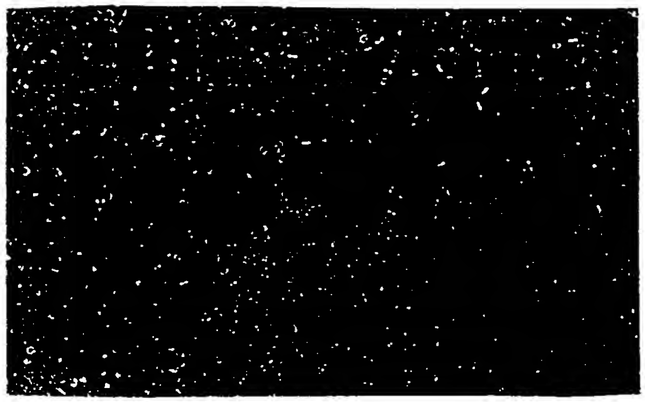
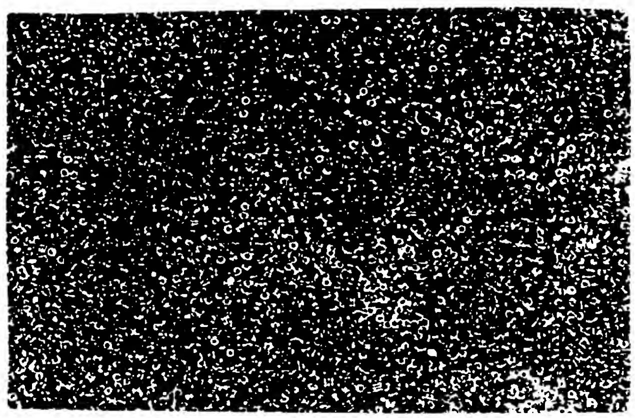


Fig. 3



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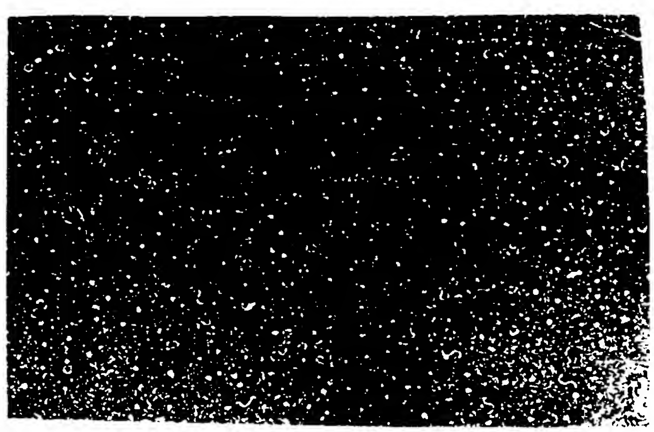
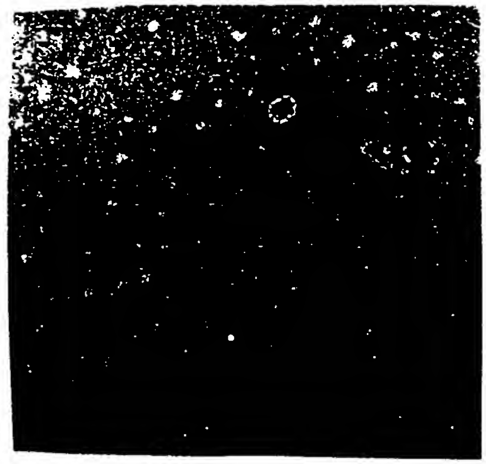


Fig. 5



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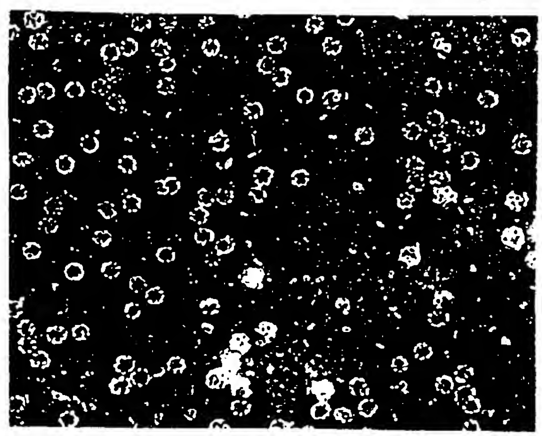
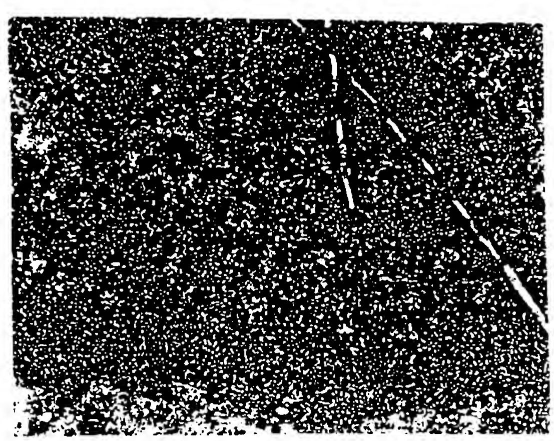


Fig. 7



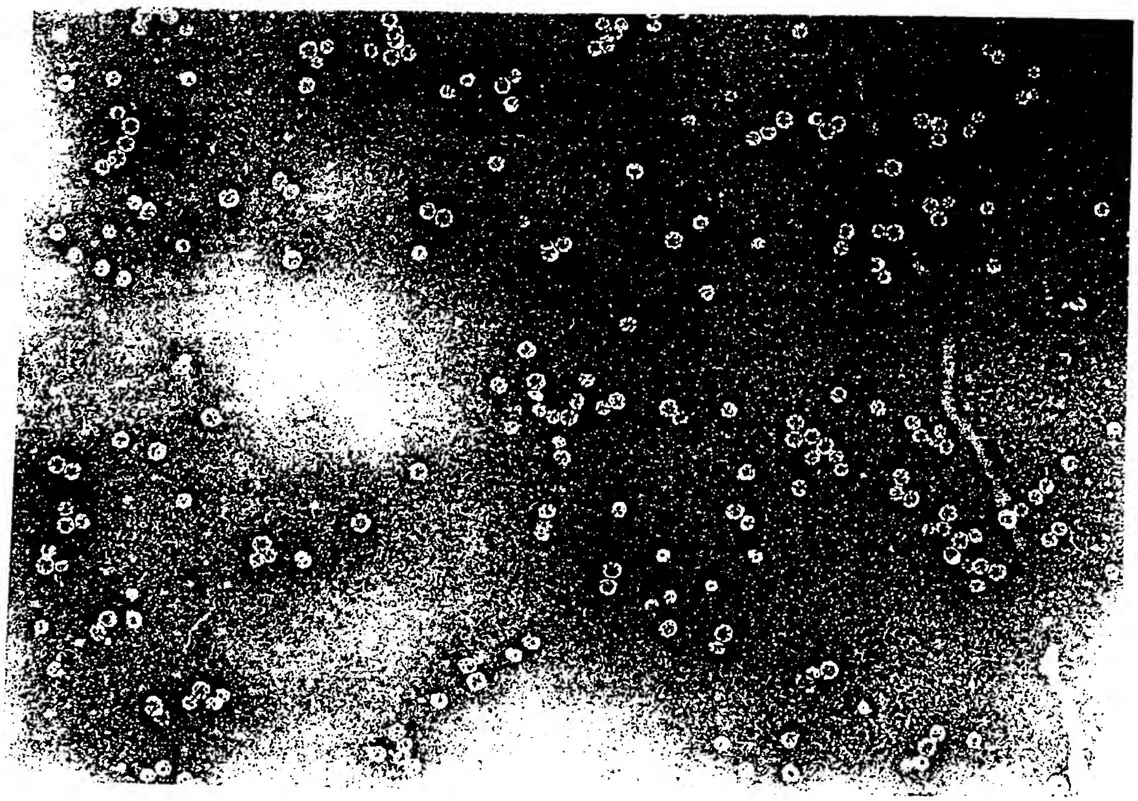
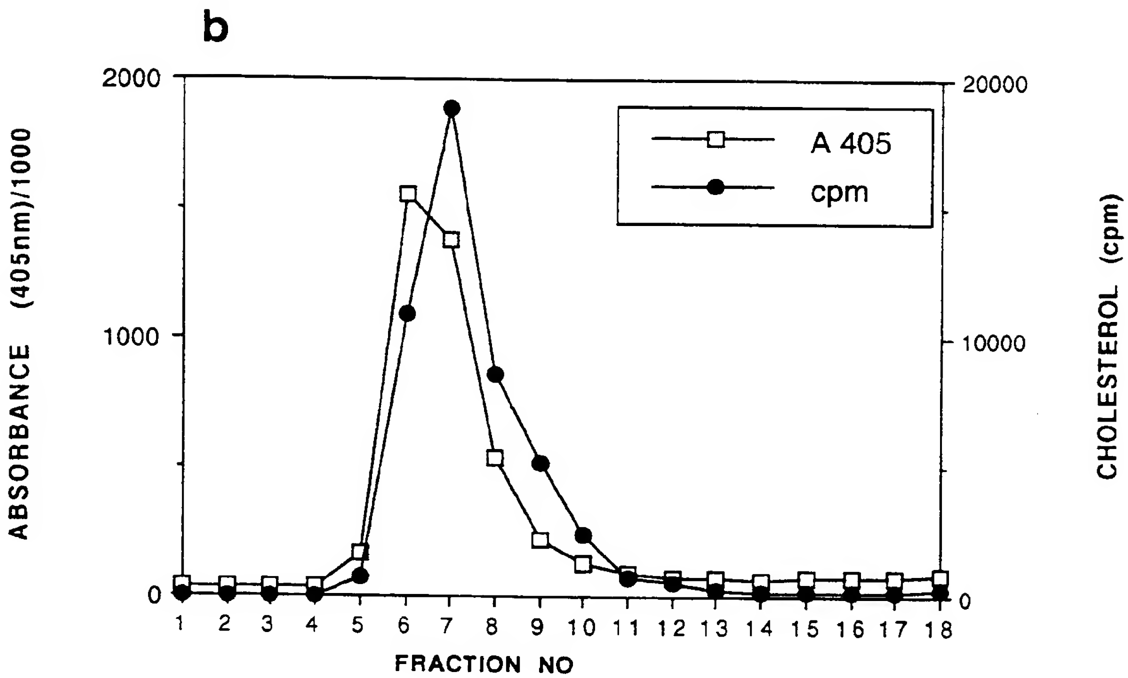


Fig. 8

Fig. 10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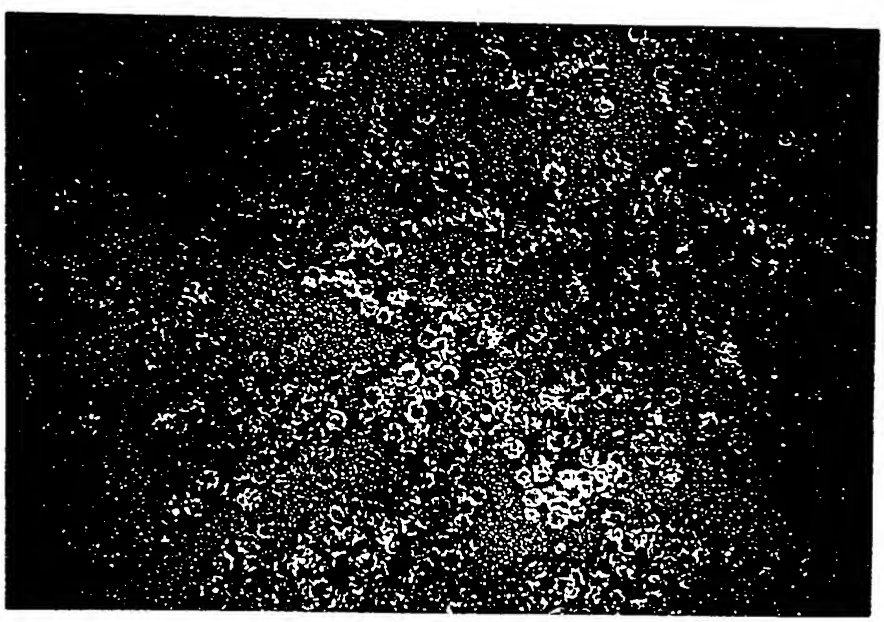
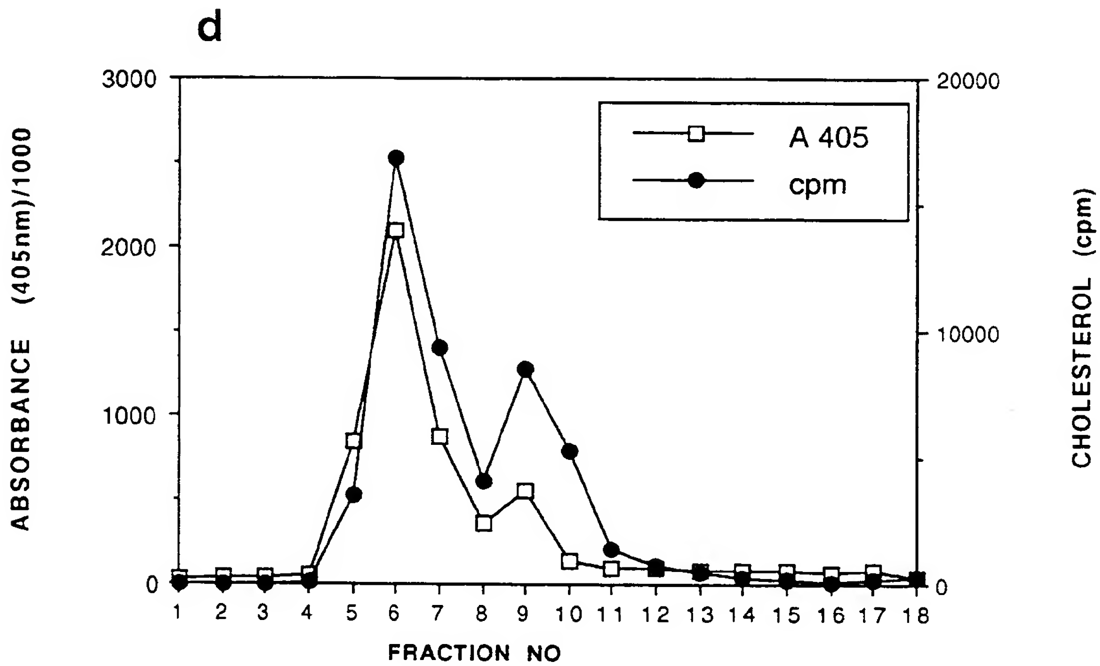


Fig. 9

Fig. 12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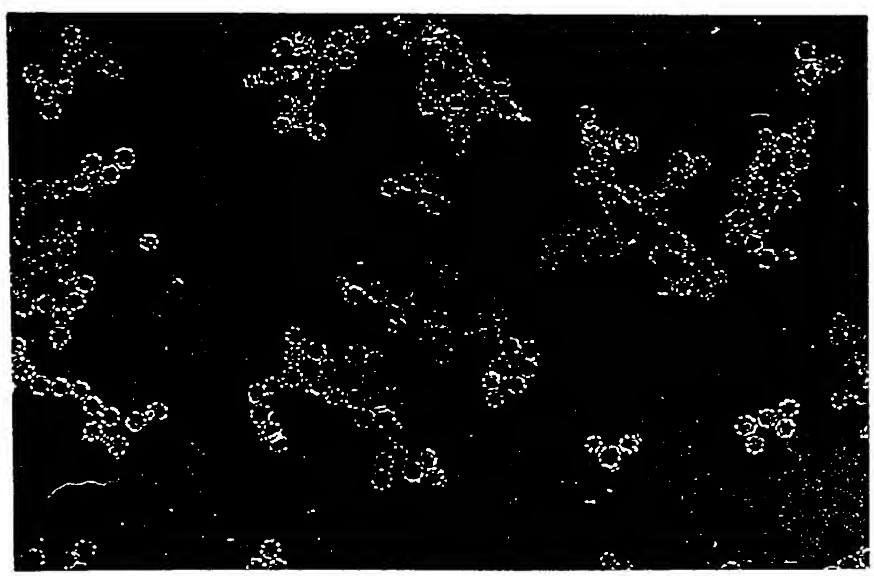

Fig. 11

26

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(11) EP 0 636 364 B1

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(22) Date of filing: **27.07.1994**

(54) **Rapidly disintegrating pharmaceutical dosage form and process for preparation thereof**

Schnellauflösliche pharmazeutische Dosierungsformen und Verfahren zu ihrer Herstellung

Formes de dosage pharmaceutiques à délitement rapide et procédé pour leur préparation

(84) Designated Contracting States:
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SI

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EP-A- 0 523 847
US-A- 4 716 041
US-A- 5 198 228

EP 0 636 364 B1

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a rapidly disintegrating pharmaceutical dosage form containing coated pharmaceutical particles and to a process for preparing such dosage forms.

BACKGROUND OF THE INVENTION

[0002] Rapidly disintegrating or dissolving pharmaceutical dosage forms are available for human patients who have difficulty swallowing conventional tablets or capsules, and for the sublingual and buccal administration of drugs.

[0003] Freeze-dried or lyophilized dosage forms are generally known to rapidly dissolve or disintegrate in the mouth. These forms consist of a porous matrix of a water-soluble or water-dispersible carrier material which is impregnated with a unit dose of the pharmaceutical active. These dosage forms are prepared by first adding the pharmaceutical active to a solution comprising the carrier material and a suitable solvent, typically water. The resulting composition is then subjected to a freeze drying procedure whereby the solvent sublimes under a high vacuum.

[0004] While freeze-dried dosage forms dissolve rapidly, they must be manufactured on expensive lyophilization equipment. Further, these dosage forms have generally only been used with water-insoluble actives that are relatively tasteless, because they disintegrate in the mouth, rather than being swallowed as in the case of conventional tablets and capsules.

[0005] Water-soluble drugs are generally avoided in freeze-dried dosage forms because of the dissolution of the drug in the mouth, which results in a bitter or otherwise objectionable taste. Further problems can arise when water-soluble drugs are used because of the formation of eutectic mixtures, which lower the freezing point of the formulation, resulting in incomplete freezing or melting during the freeze-drying process. This phenomenon results in product loss.

[0006] M. S. Amer in U.S. Patent 4,866,046, issued September 12, 1989, describes an aspirin tablet that rapidly dissolves in the oral, preferably sublingual, cavity within 2-60 seconds. This tablet provides rapid absorption of aspirin from the saliva into the blood stream. The sublingual tablet is prepared by compressing into slugs a mixture of starch (10% moisture), acetylsalicylic acid, flavor and sweetener. The slugs are then ground (14-16 Mesh size) and recompressed into tablets. An amino acid may also be used with the aspirin for its solubilizing and a taste-neutralizing effects.

[0007] U.S. Patent No. 5,082,667, issued January 21, 1992, to K. G. Van Scoik discusses a tablet triturate dosage that quickly dissolves in the buccal cavity. The form includes a porous, cementatory network of a water-soluble but ethanol-insoluble carbohydrate, which contains discrete particles of the active ingredient that have been coated with a triglyceride coating. The discrete particles are prepared by suspending the active ingredient in molten triglyceride. The discrete particles are mixed with the carbohydrate and a temporary liquid binder to form a damp mass. The mass is then shaped into a tablet and dried to form the tablet triturate.

[0008] The tablet triturate of Van Scoik is limited to active ingredients, such as estazolam, that are not sensitive to the melting temperature of the triglyceride. Further, since the dosage form is formed into a damp mass and subsequently dried, conventional, compression tableting machines cannot be used to manufacture this product.

[0009] J. A. McCarty, in U.S. Patent No. 5,112,616, issued May 12, 1992, discusses a fast dissolving buccal tablet containing a buccally absorbable active ingredient, a pharmaceutically acceptable lubricant and a soluble, directly compressible tablet excipient, such as sucrose or lactose. These ingredients are mixed together and compressed into the final tablet form. Since the active ingredient is not coated, patient compliance, especially in children, would be an issue if the pharmaceutical had a bitter or otherwise objectional taste.

[0010] A need, therefore, exists for a rapidly disintegrating dosage form containing taste-masked pharmaceutical particles that can be manufactured without the use of water or solvents, and compressed on conventional tableting machines. This dosage form should be suitable for use with both water-soluble and water-insoluble actives which may have an objectional taste.

SUMMARY OF THE INVENTION

[0011] The present invention provides a compressed pharmaceutical dosage form containing at least one pharmaceutical particle coated with a taste-masking composition, a water-disintegratable, compressible carbohydrate and a binder. These components are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to cause the carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing the coated pharmaceutical particle to be swallowed.

[0012] In a preferred embodiment, the pharmaceutical is coated with a blend of a first polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate and a second polymer selected from the group consisting of polyvinyl pyrrolidone and hydroxypropyl cellulose, where the weight ratio of the first polymer to the second pol-

ymer is within the range of about 90:10 to about 50:50.

[0013] In a further preferred embodiment of the present invention, the compressed pharmaceutical dosage form is prepared by coating the pharmaceutical with the aforementioned blend of first and second polymers in a fluidized bed coating operation. The coated pharmaceutical is dry blended with the water-disintegratable, compressible carbohydrate and the binder, and then compressed into a wafer having a hardness within the range of about 1.0 to about 3.0 kp, whereby the carbohydrate disintegrates after oral administration allowing said coated pharmaceutical to be swallowed.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0014] The compressed pharmaceutical dosage forms of the present invention rapidly disintegrates when contacted by water, saliva and aqueous solutions, and are particularly useful in the oral delivery of drugs. As used in the present invention "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with the aforementioned fluids. These dosage forms generally disintegrate in the mouth within about 30 seconds, and preferably within about 20 seconds or less.

[0015] The dosage forms contain coated particles comprising at least one pharmaceutical coated with a taste-masking coating, a water-disintegratable, compressible carbohydrate, and a binder. These ingredients are dry blended and then compressed into a mass, preferably a wafer, having a hardness sufficient to cause the carbohydrate to disintegrate after oral administration. Upon disintegration, the coated pharmaceutical particles are released from the dosage form with no objectionable taste and swallowed by the user.

[0016] Conventional tableting machines can be used to compress the ingredients into the final dosage form. Since the ingredients are dry blended, water-soluble, as well as water-insoluble, coated pharmaceuticals can be used in the dosage form. Further, in view of the use of a taste-masking coating, pharmaceuticals having an objectional taste may also be used in the present invention.

[0017] The water-disintegratable, compressible carbohydrate used in the present invention includes carbohydrate materials conventionally used in tablets. The carbohydrates facilitate the breakup of the dosage form after oral administration, and are described in Liberman et al., Pharmaceutical Dosage Forms, Marrel Dekker, Inc., New York, 2 Ed. Vol. 1, pp. 205-209 (1990). Preferred water-disintegratable, compressible carbohydrates include mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, and mixtures thereof.

[0018] The binder in the present invention is used to add cohesiveness to the formulation, thereby providing the necessary bonding to form a cohesive mass or compact upon compression. These binders are conventionally used in direct compression tablets and are described in Liberman et al., Pharmaceutical Dosage Forms, 2 Ed., Vol. 1, pp. 209-214 (1990). Preferred binders include cellulose, cellulosic derivatives, polyvinyl pyrrolidone, starch, modified starch, and mixtures thereof, and, in particular, microcrystalline cellulose available from FMC Corp. under the trademark AVICEL® PH 101.

[0019] The dosage form of the present invention contains a coated particle containing at least one pharmaceutical active coated with a taste-masking coating. The active may be coated with taste-masking coatings known in the art, such as those described in U.S. Patent No. 4,851,226, issued July 25, 1989, to T.W. Julian, et al.,; U.S. Patent No. 5,075,114, issued December 24, 1991 to E.J. Roche; and EP-A-0 523 847. As used in the present invention, "coated particle" refers to a solid pharmaceutical in the form of a crystal or particle, an agglomerate of individual particles, or a granuled particle, which has been coated with the taste-masking composition. The dosage form may provide for immediate or sustained release of the pharmaceutical active.

[0020] Taste-masking compositions suitable for use as coatings are provided in the following Table:

Polymer System	Coat Level[1]	Polymer Ratio[2]
Cellulose Acetate/PVP	5-60%	90/10 to 60/40
Cellulose Acetate Butyrate/PVP	5-60%	90/10 to 60/40
Cellulose Acetate/HPC	5-60%	90/10 to 50/50
Cellulose Acetate Butyrate/HPC	5-60%	90/10 to 50/50
Cellulose Acetate/EUDRAGIT E100	8-60%	All ratios
Cellulose Acetate Butyrate/EUDRAGIT E 100	8-60%	All ratios
Ethyl Cellulose/PVP	8-60%	90/10 to 60/40
Ethyl Cellulose/HPC	8-60%	90/10 to 50/50
Ethyl Cellulose/EUDRAGIT E 100	8-60%	All ratios
HPC	10-60%	NA
HEC	10-60%	NA
EUDRAGIT E 100	10-60%	NA
HPMC	10-60%	NA
HEC/HPMC	10-60%	All ratios
HPC/HPMC	10-60%	All ratios
HEC/HPC	10-60%	All ratios
2-vinyl pyridine styrene co-polymer	10-60%	NA
CA/2-vps	8-60%	All ratios
CAB/2-vps	8-60%	All ratios
Ethyl Cellulose/2-vps	8-60%	All ratios
Cellulose Triacetate/PVP	8-60%	90/10 to 60/40
Cellulose Triacetate/HPC Cellulose Triacetate/<->	8-60%	90/10 to 50/50
EUDRAGIT E 100	8-60%	All ratios

PVP - polyvinylpyrrolidone
HPC - Hydroxypropyl cellulose
HEC - Hydroxyethyl cellulose
HPMC - Hydroxypropylmethyl cellulose
CA - Cellulose Acetate
CAB - Cellulose Acetate Butyrate
2-VPS - 2-Vinyl pyridine styrene
EUDRAGIT™ E-100 - methylaminoethyl-methacrylate and neutral methacrylic acid esters available from Rohm Pharma GmbH, Germany.

[1] Percent by weight of the coated particle in a dried state.
[2] By weight.

[0021] Substantially all of the pharmaceutical or granulated pharmaceutical should be coated with a layer of taste-masking composition having a thickness of about 3 to about 10 μm. The coating should be substantially free of cracks, holes or other imperfections when examined under a scanning electron microscope at 100-500×.

[0022] The pharmaceutical active is preferably coated with a blend of a first polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate and a second polymer selected from the group consisting of

polyvinyl pyrrolidone and hydroxypropyl cellulose. The weight ratio of the first polymer to the second polymer in this blend is within the range of about 90:10 to about 50:50 and preferably about 90:10 to about 70:30.

[0023] The first polymer of the blend is generally water-insoluble, but is soluble in organic solvents. These polymers provide good taste-masking properties since they do not dissolve in the mouth. However, if used alone, they do not provide adequate bioavailability of the pharmaceutical. To provide the requisite bioavailability, the second polymer, which is soluble in both water and organic solvents, is added to the blend that is used to coat the pharmaceutical active. This blend of first and second polymers provides the balance needed for the taste masking.

[0024] Preferred blends of the first and second polymers include cellulose acetate (CA) and polyvinyl pyrrolidone (PVP) having a weight ratio of CA:PVP within the range of about 90:10 to about 60:40, cellulose acetate (CA) and hydroxypropyl cellulose (HPC) having a weight ratio of CA:HPC within the range of about 90:10 to about 50:50, cellulose acetate butyrate (CAB) and hydroxypropyl cellulose (HPC) having a weight ratio of CAB:HPC within the range of about 90:10 to about 50:50, and cellulose acetate butyrate (CAB) and polyvinyl pyrrolidone (PVP) having a weight ratio of CAB:PVP within the range of about 90:10 to about 60:40.

[0025] Cellulose acetate NF powder, e.g., CA 398-10, CA 320-S or CA 435-75S available from FMC Corp., may be used as the first polymer in the blend. CA 398-10 polymer has an acetyl content of about 39.8 weight percent, a hydroxyl content of about 3.4 weight percent, a degree of substitution of 2.7 and a solution viscosity of about 38 poises or 10 seconds, as determined by ASTM Method D 1343 in the solution described as Formula A, ASTM Method D 871. The typical weight average molecular weight, according to the manufacturer, is 177,000 and the typical number average molecular weight is 58,500. CA 320-S polymer has an acetyl content of about 32.0 weight percent, a hydroxyl content of about 9.0 weight percent and a degree of substitution of 2.1. In a solution of 90:10 CH_2Cl_2:methanol, at 4%(w/w) concentration, the viscosity is 50 centipoise. The typical weight average molecular weight is 100,500 and the typical number average molecular weight is 63,500. CA 435-75S has an acetyl content of about 43.6 weight percent and a hydroxyl content of about 0.9 weight percent.

[0026] Cellulose acetate butyrate, e.g., CAB 171-15S, CAB 381-2 and CAB 500-1 available from FMC Corp., may also be used as the first polymer. CAB 171-15S has a butyryl content of 17 weight percent, an acetyl content of 29.5 weight percent, a hydroxyl content of 1.5 weight percent and a viscosity of 24 centipoises in a 4 weight percent solution of methylene chloride:methanol (90:10) one day after solution preparation at 25°C. CAB 381-2 has a butyryl content of 37 weight percent, an acetyl content of 13 weight percent and a hydroxyl content of 1.5 weight percent. CAB 500-1 has a butyryl content of 50 weight percent, an acetyl content of 5 weight percent and a hydroxyl content of 0.5 weight percent.

[0027] Polyvinyl pyrrolidone (Povidone USP), e.g., PLASDONE® K-25, K-25/28 or K-29/32 from ISP Corporation, may be used as the second polymer in the blend. Povidone K-25 has a viscosity of 2.4 centipoises in a 5% solution of water at a pH 7 and 25°C.

[0028] Hydroxypropyl cellulose, e.g., KLUCEL EF, JF and LF, available from Aqualon Co. may also be used a the second polymer. These polymers generally have a molecular weight of about 80,000 to about 370,000.

[0029] The blend of first and second polymers may be coated directly onto the pure pharmaceutical or may be coated onto a granulated particle containing the pharmaceutical. In the case of a granulated particle, such as a rotogranulated particle, the pharmaceutical active will constitute from about 5 to about 90 weight percent of the particle, with the remainder being the binder or filler. Suitable binders for the granulated particles include polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and other pharmaceutically acceptable polymers. Fillers suitable for use in such granulated particles include lactose, confectioner's sugar, mannitol, dextrose, fructose, other pharmaceutically acceptable saccharides and microcrystalline cellulose.

[0030] The coated particles are prepared by spraying an organic solvent solution of the polymeric blend onto the pharmaceutical, or a granulated particle containing the pharmaceutical, in a fluidized bed, such as a Wurster coater or a rotogranulator. A wide variety of organic solvents may be used to prepare the solution of the polymeric blend. For example, a preferred solvent is a mixture of acetone and methanol, but other solvent systems may be employed, including methylene chloride, methylene chloride-methanol, acetone-ethyl acetate, toluene-ethanol and acetone-ethanol. Generally, the proportion of the polymer blend in the solvent solution will be within the range of about 5 to about 20, preferably about 8 to about 15, weight percent, depending on the solvent and other similar considerations.

[0031] When a fluidized bed coating operation is used, air, which may be heated, passes through a bed of the pharmaceutical solids to fluidize them, and the solution of the polymeric blend is sprayed onto the fluidized bed and thereby coats the pharmaceutical. The air passing through the bed dried the coating onto the pharmaceutical, so that a dry coated granule is obtained.

[0032] Conventional fluidized bed coating equipment is used in the present invention to coat the pharmaceutical or the rotogranulated particle containing the pharmaceutical. This equipment includes Wurster fluid-bed coaters, where the solution of the polymer blend is sprayed from the bottom of the chamber, and a rotogranulator, where the solution of the polymer blend is tangentially sprayed. These coating operations are further described in Liberman et al., Pharmaceutical Dosage Forms, Marrel Dekker, Inc., New York, Vol. 3, pp. 138-150 (1990).

[0033] The coated particle, in a dried state, generally contains about 5 to about 60, preferably about 10 to 40, weight percent of the blend of the first and second polymers. The exact proportions of the coating to the pharmaceutical can, however, vary depending upon the level of taste-masking required and whether a sustained or immediate release of the pharmaceutical is desired. Larger proportions of the coating tend to provide a sustained release effect and enhance taste-masking.

[0034] The dosage form of the present invention may be used to orally administer a wide variety of solid pharmaceutical actives. Pharmaceutical actives which can be used in the dosage form include acetaminophen, ibuprofen, flurbiprofen, naproxen, aspirin, pseudoephedrine, phenylpropanolamine, chlorpheniramine maleate, dextromethorphan, diphenhydramine, famotidine, loperamide, ranitidine, cimetidine, astemizole, terfenadine, terfenadine carboxylate, cetirizine, mixtures thereof and pharmaceutically acceptable salts thereof.

[0035] The pharmaceutical(s) present in the dosage form in a therapeutic effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular compound being administered, the bioavailability characteristics of the pharmaceutical, the dose regime, the age and weight of the patient, and other factors must be considered.

[0036] The dosage form may also contain ingredients other than the coated particles, carbohydrate and binder. The additional ingredients include sweeteners, such as aspartame, sucralose and saccharin; and lubricants, such as magnesium stearate, stearic acid, talc, and waxes. The dosage form may also incorporate pharmaceutical acceptable adjuvants. Such adjuvants, include, for example, preservatives, flavors, antioxidants, surfactants, and/or colors.

[0037] The compressed dosage form, on a dry basis, generally comprises from about 0.1 to about 45, preferably about 12 to about 25, percent by weight of the coated pharmaceutical particle; from about 30 to about 90, preferably about 40 to about 65, percent by weight of the water-disintegratable, compressible carbohydrate material; from about 1 to about 30, preferably about 5 to about 20, percent by weight of the binder; from about 0.1 to about 5, preferably about 0.1 to about 0.5, percent by weight of the lubricant; from about 0.05 to about 5, preferably about 0.1 to about 3.0, percent by weight of the sweetener; from about 0.05 to about 5, preferably about 0.2 to about 2.0, percent by weight of the flavor; and from about 0.01 to about 5, preferably about 0.03 to about 0.3, percent by weight of the color.

[0038] The unit weight of the dosage form will vary depending on the dosage of the active ingredient. The unit weight will generally range from about 250 to about 1500, preferably about 250 to about 1000, mg. A typical dosage form may contain:

Ingredient	Unit Wt. (mg)
Coated Pharmaceutical Particle	0.5 - 600
Compressible Carbohydrate	250 - 750
Binder	20 - 100
Lubricant	4 - 10
Sweetener	1 - 10
Flavor	1 - 10
Color	1 - 10

[0039] In a preferred embodiment of the invention, the dosage form has a size, shape, weight and hardness that allows for it to be introduced into the oral cavity and placed on the tongue, so as to rapidly disintegrate. Generally, the dosage form will be a tablet having a coin-shaped disc or wafer configuration. Preferably, the wafer will have a diameter of about 1.48 cm (7/16 inch) to about 1.91 cm (3/4 inch), preferably about 1.59 cm (5/8 inch), and a thickness of about 0.13 cm (0.05 inch) to about 1.27 cm (0.5 inch), preferably about 0.20 cm (0.08 inch) to 0.64 cm (0.25 inch). While a wafer shape is generally preferred, because it provides a larger surface area to be contacted by the tongue and other moist areas of the oral cavity, other shapes may be employed, such as a cube, triangle and cylinder.

[0040] The dosage form is prepared by forming the coated particles of the pharmaceutical using the aforementioned techniques. The particle size of the coated particles, as well as the remaining components, is generally less than 400, preferably less than 150, μm. Larger particle sizes tend to give the wafer a gritty mouth feel, and should therefore be avoided. The components of the dosage form are then dry mixed to form a uniform powder blend. The blend is then compressed into a mass having the desired shape and hardness using conventional compression tableting techniques.

[0041] The external pressure applied by the tablet press during the compression step is controlled so that the hardness of the dosage form is within the range of about 1.0 to about 3.0, preferably about 1.5 to about 2.5, kp (kiloponds)

. This hardness is measured by conventional pharmaceutical hardness testing equipment, such as a Schleuniger Hardness Tester. Hardnesses within this range provide a dosage form which will rapidly disintegrate when placed in the oral cavity. If the hardness exceeds 3.0 kp, the compressed dosage form will not readily disintegrate in the oral cavity, while hardnesses less than 1.0 kp result in a dosage form exhibiting high friability.

[0042] Specific embodiments of the present invention are illustrated by way of the following examples. This invention is not confined to the specific limitations set forth in these examples, but rather to the scope of the appended claims. Unless otherwise stated, the percentages and ratios given below are by weight.

EXAMPLE

[0043] This Example provides a formulation for making a rapidly disintegrating, compressed wafer that contains acetaminophen coated with a blend of cellulose acetate and polyvinyl pyrrolidone. The weights provided hereinafter are based on a wafer unit weight of 400 mg.

[0044] A coating solution containing a blend of cellulose acetate (CA 398-10) and polyvinyl pyrrolidone (Povidone 29/32) was prepared at 12 % solids with an acetone/methanol (80:20) solvent. The ratio of cellulose acetate to polyvinyl pyrrolidone was 85:15.

[0045] Four kilograms of acetaminophen (nominal particle size of 300 µm) was charged into a Wurster (bottom spray) fluidized bed coating apparatus. The acetaminophen was then placed in a fluidized state by a flow of air at a temperature of 30°C. The coating solution was then sprayed (atomization air pressure = 3 bar) onto the fluidized acetaminophen particles at a rate of 80 grams/min. until a coated acetaminophen particle containing approximately 12 % by weight of the coating was obtained.

[0046] The coated acetaminophen particles were combined with following ingredients to produce the wafers:

Ingredients	Unit Wt. (mg)
CA/PVP Coated Acetaminophen Particles	91.0
Mannitol (Granular), USP	229.15
Microcrystalline Cellulose, NF	60.0
Aspartame, NF	6.0
Prosweet Powder (Sugarless)	1.5
Color	0.9
Citric Acid, USP	3.0
Flavors	5.2
Colloidal Silicon Dioxide	0.25
Stearic Acid, NF	3.0
Wafer Weight	400.0

Dry Blending

[0047]

1. Screen the color through a 60 mesh screen, the CA/PVP coated acetaminophen particles through a 30 mesh screen and the mannitol through a 12 mesh screen.

2. Mix the microcrystalline cellulose, aspartame, flavors, citric acid, Prosweet, colloidal silicon dioxide and stearic acid by shaking in a container for two minutes.

3. Blend the color and mannitol in a blender.

4. Place the mixture from Step 2 and the CA/PVP coated acetaminophen particles in blender containing the mixture from Step 3 and blend.

Tablet Compression

[0048]

1. Compress the blend into wafers to the following specifications on a rotary tablet press equipped with the following tooling:

   Punches: 1.59 cm (5/8 inch), flat faced, bevel edge
   Dies: 1.59 cm (5/8 inch) round
   Group Weight (10 wafers): Target - 4.0 grams
   (Range: 360 - 440 milligrams)
   Thickness: Target 2.0 mm (Range 1.8 to 2.2 mm)
   Hardness: Target 2 kp (Range 1.5 to 2.5 kp)

2. Collect compressed wafers into a properly labelled container.

[0049] A wafer was placed in on the tongue of a human and was found to disintegrate in less than 30 seconds without a bitter aftertaste.
[0050] Various modifications can be made from the above-described embodiments without departing from the scope of the present invention.

Claims

1. A compressed pharmaceutical dosage form, comprising:

   at least one coated particle comprising at least one pharmaceutical coated with a taste-masking coating;
   a water-disintegratable, compressible carbohydrate; and
   a binder,
   said dosage form having a hardness within the range of about 1.0 to about 3.0 kp and sufficient to cause said carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing said particle to be swallowed.

2. The pharmaceutical dosage form of claim 1 wherein the compressible carbohydrate is mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, or a mixture thereof.

3. The pharmaceutical dosage form of claim 1 or claim 2 wherein said coated particle comprises at least one pharmaceutical coated with a blend of a first polymer which is a cellulose acetate or cellulose acetate butyrate and a second polymer which is polyvinyl pyrrolidone or hydroxypropyl cellulose, wherein the weight ratio of the first polymer to the second polymer is within the range of about 90:10 to about 50:50.

4. A pharmaceutical dosage form of any one of claims 1 to 3 being a compressed wafer, comprising:

   coated particles comprising at least one pharmaceutical coated with a blend of a first polymer which is a cellulose acetate or cellulose acetate butyrate and a second polymer which is polyvinyl pyrrolidone or hydroxypropyl cellulose, wherein the weight ratio of the first polymer to the second polymer is within the range of about 90:10 to about 50:50;
   a water-disintegratable, compressible carbohydrate which is mannitol, sorbitol, dextrose, sucrose, xylitol, lactose, or
   a mixture thereof; and
   a binder which is cellulose, a cellulosic derivative, polyvinyl pyrrolidone, starch, modified starch or a mixture thereof,
   said wafer having a hardness within the range of about 1.0 to about 3.0 kp whereby said carbohydrate disintegrates after oral administration, allowing said coated particles to be swallowed.

5. The wafer of claim 4 having a diameter of about 1.48 cm (7/16 inch) to about 1.91 cm (3/4 inch), a thickness of about 0.13 cm (0.05 inch) to about 1.27 cm (0.5 inch), and a hardness of about 1.5 to about 2.5 kp.

6. The wafer of claim 4 or claim 5 comprising:

about 0.5 to about 600 mg of said coated particles;
about 250 to about 750 mg of said carbohydrate; and
about 20 to about 100 mg of said binder,

and which optionally additionally comprises:

about 4 to about 10 mg of a lubricant;
about 1 to about 10 mg of a color;
about 1 to about 10 mg of a sweetener; and
about 1 to about 10 of a flavor.

7. The pharmaceutical dosage form of any one of claims 3 to 6 wherein the coated particle comprises about 5 to about 60 percent by weight of the blend of first and second polymers.

8. The pharmaceutical dosage form of any one of claims 1 to 7 wherein the pharmaceutical is acetaminophen, ibuprofen, flurbiprofen, naproxen, asprin, pseudoephedrine, phenylpropanolamine, chlorpheniramine maleate, dextromethorphan, diphenhydramine, famotidine, loperamide, ranitidine, cimetidine, astemizole, terfenadine, terfenadine carboxylate, certirizine, a pharmaceutically acceptable salt thereof or a mixture thereof, and wherein preferably the pharmaceutical is acetaminophen, ibuprofen, loperamide, famotidine or aspirin.

9. A process for preparing a compressed pharmaceutical dosage form, comprising the steps of:

forming at least one coated particle comprising at least one pharmaceutical coated with a taste-masking coating;
dry mixing said coated particle with a water-disintegratable, compressible carbohydrate and a binder; and
compressing the mixture into a mass having a hardness sufficient to cause said carbohydrate to disintegrate within 30 seconds after oral administration, thereby allowing said coated particle to be swallowed;
wherein said compressed pharmaceutical dosage form has a hardness within the range of about 1.0 to about 3.0 kp.

Patentansprüche

1. Gepreßte pharmazeutische Dosierungsform, umfassend: wenigstens einen überzogenen Partikel, der wenigstens ein Pharmazeutikum umfaßt, das mit einer geschmacksmaskierenden Beschichtung überzogen ist; ein in Wasser zerfallendes, preßbares Kohlenhydrat; und ein Bindemittel, wobei die Dosierungsform eine Härte im Bereich von etwa 1,0 bis 3,0 kp und ausreichend aufweist, um zu bewirken, daß das Kohlenhydrat innerhalb 30 Sekunden nach oraler Verabreichung zerfällt und dadurch ermöglicht, daß der Partikel geschluckt wird.

2. Pharmazeutische Dosierungsform nach Anspruch 1, bei der das preßbare Kohlenhydrat Mannitol, Sorbitol, Dextrose, Saccharose, Xylitol, Lactose oder eine Mischung daraus ist.

3. Pharmazeutische Dosierungsform nach Anspruch 1 oder Anspruch 2, bei der der überzogene Partikel wenigstens ein Pharmazeutikum umfaßt, das mit einer Mischung aus einem ersten Polymer, das ein Zelluloseacetat oder Zelluloseacetatbutyrat ist, und einem zweiten Polymer, das Polyvinylpyrrolidon oder Hydroxypropylzellulose ist, überzogen ist, wobei das Gewichtsverhältnis des ersten Polymers zu dem zweiten Polymer im Bereich von etwa 90:10 bis etwa 50:50 liegt.

4. Pharmazeutische Dosierungsform nach einem der Ansprüche 1 bis 3, die ein gepreßtes Plättchen ist, umfassend:

überzogene Partikel, die wenigstens ein Pharmazeutikum umfassen, das mit einer Mischung aus einem ersten Polymer, das Zelluloseacetat oder oder Zelluloseacetatbutyrat ist, und einem zweiten Polymer, das Polyvinylpyrrolidon oder Hydroxypropylzellulose ist, überzogen ist, wobei das Gewichtsverhältnis des ersten Polymers zum zweiten Polymer im Bereich von etwa 90:10 bis etwa 50:50 liegt; ein in Wasser zerfallendes, preßbares Kohlenhydrat, das Mannitol, Sorbitol, Dextrose, Saccharose, Xylitol, Lactose oder eine Mischung daraus ist; und
ein Bindemittel, das Zellulose, ein Zellulosederivat, Polyvinylpyrrolidon, Stärke, modifizierte Stärke oder eine Mischung daraus ist, wobei das Plättchen eine Härte im Bereich von 1,0 bis etwa 3,0 kp aufweist, wodurch das Kohlenhydrat nach oraler Verabreichung zerfällt und ermöglicht, daß die überzogenen Partikel geschluckt wer-

den.

5. Plättchen nach Anspruch 4, das einen Durchmesser von etwa 1,48 cm (7/16 Inch) bis etwa 1,91 cm (3/4 Inch), eine Dicke von etwa 0,13 cm (0,05 Inch) bis etwa 1,27 cm (0,5 Inch) und eine Härte von 1,5 bis 2,5 kp aufweist.

6. Plättchen nach Anspruch 4 oder Anspruch 5, umfassend:

   etwa 0,5 bis etwa 600 mg der überzogenen Partikel; etwa 250 bis etwa 750 mg des Kolenhydrates; und etwa 20 bis etwa 100 mg des Bindemittels, und das optional zusätzlich umfaßt: etwa 4 bis etwa 10 mg eines Schmiermittels, etwa 1 bis etwa 10 mg eines Farbstoffes, etwa 1 bis etwa 10 mg eines Süßstoffes; und etwa 1 bis etwa 10 mg eines Aromas.

7. Pharmazeutische Dosierungsform nach einem der Ansprüche 3 bis 6, bei der der überzogene Partikel etwa 5 bis etwa 60 Gew.-% der Mischung aus erstem und zweitem Polymer umfaßt.

8. Pharmazeutische Dosierungsform nach einem der Ansprüche 1 bis 7, bei der das Pharmazeutikum Acetaminophen, Ibuprofen, Flurbiprofen, Naproxen, Aspirin, Pseudoephedrin, Phenylpropanolamin, Chlorpheniraminmaleat, Dextromethorphan, Diphenhydramin, Famotidin, Loperamid, Ranitidin, Cimetidin, Astemizol, Terfenadin, Terfenadinecarboxylat, Certirizin, ein pharmazeutisch annehmbares Salz davon oder eine Mischung daraus ist, und bei der das Pharmazeutikum vorzugsweise Acetaminophen, Ibuprofen, Loperamid, Famotidin oder Aspirin ist.

9. Verfahren zur Herstellung einer gepreßten pharmazeutischen Dosierungsform, das die Schritte umfaßt von:

   Bilden wenigstens eines überzogenen Partikels, der wenigstens ein Pharmazeutikum umfaßt, das mit einer geschmacksmaskierenden Beschichtung überzogen ist; trockenes Mischen des überzogenen Partikels mit einem in Wasser zerfallenden, preßbaren Kohlenhydrat und einem Bindemittel; und Pressen der Mischung in eine Masse, die eine ausreichende Härte aufweist, um zu bewirken, daß das Kohlenhydrat innerhalb 30 Sekunden nach oraler Verabreichung zerfällt und dadurch ermöglicht, daß die überzogenen Partikel geschluckt werden; wobei die gepreßte pharmazeutische Dosierungsform eine Härte im Bereich von etwa 1,0 bis etwa 3,0 kp aufweist.

Revendications

1. Forme de dosage pharmaceutique à l'état comprimé, comprenant: au moins une particule enrobée comprenant au moins un produit pharmaceutique enrobé d'un enrobage donnant du goût;

   un carbohydrate compressible, désintégrable à l'eau; et
   un liant,
   ladite forme de dosage ayant une dureté dans la gamme d'environ 1,0 à environ 3,0 kp et suffisante pour forcer ledit carbohydrate à se désintégrer dans les 30 secondes après administration orale pour ainsi permettre à ladite particule d'être avalée.

2. Forme de dosage pharmaceutique de la revendication 1, où le carbohydrate compressible est du mannitol, du sorbitol, du dextrose, du saccharose, du xylitol, du lactose ou un mélange de ceux-ci.

3. Forme de dosage pharmaceutique de la revendication 1 ou 2, où ladite particule enrobée comprend au moins un produit pharmaceutique enrobé d'un mélange d'un premier polymère qui est un acétate de cellulose ou un acétate butyrate de cellulose et un second polymère qui est de la polyvinyl pyrrolidone ou de l'hydroxypropyl cellulose, où le rapport pondéral du premier polymère au second polymère est dans la gamme d'environ 90:10 à environ 50:50.

4. Forme de dosage pharmaceutique selon l'une quelconque des revendications 1 à 3 qui est une pastille comprimée, comprenant:

   des particules enrobées comprenant au moins un produit pharmaceutique enrobé d'un mélange d'un premier polymère qui est un acétate de cellulose ou un acétate butyrate de cellulose et d'un second polymère qui est de la polyvinyl pyrrolidone ou de l'hydroxypropyl cellulose, où le rapport pondéral du premier polymère au second polymère est dans la gamme d'environ 90:10 à environ 50:50; un carbohydrate désintégrable à l'eau, compressible, qui est du mannitol, sorbitol, dextrose, saccharose, xylitol, lactose, ou leurs mélanges; et

un liant qui est de la cellulose, un dérivé cellulosique, de la polyvinyl pyrrolidone, de l'amidon, de l'amidon modifié ou un mélange de ceux-ci,
ladite pastille ayant une dureté dans la gamme d'environ 1,0 à environ 3,0 kp et ainsi ledit carbohydrate se désintègre après administration orale, permettant auxdites particules enrobées d'être avalées.

5. Pastille selon la revendication 4 ayant un diamètre d'environ 1,48 cm (7/16 pouce) à environ 1,91 cm (3/4 pouce), une épaisseur d'environ 0,13 cm (0,05 pouce) à environ 1,27 cm (0,5 pouce), et une dureté d'environ 1,5 à environ 2,5 kp.

6. Pastille de la revendication 4 ou de la revendication 5 comprenant:

   environ 0,5 à environ 600 mg desdites particules enrobées;
   environ 250 à environ 750 mg dudit carbohydrate; et
   environ 20 à environ 100 mg dudit liant,

   et qui comprend additionnellement, facultativement:

   environ 4 à environ 10 mg d'un lubrifiant;
   environ 1 à environ 10 mg d'une couleur;
   environ 1 à environ 10 mg d'un édulcorant; et
   environ 1 à environ 10 d'un arôme.

7. Forme de dosage pharmaceutique selon l'une quelconque des revendications 3 à 6 où la particule enrobée comprend environ 5 à environ 60 pour cent en poids du mélange des premier et second polymères.

8. Forme de dosage pharmaceutique selon l'une quelconque des revendications 1 à 7 où le produit pharmaceutique est acétaminophène, ibuprofène, flurbiprofène, naproxène, aspirine, pseudoéphédrine, phénylpropanolamine, maléate de chlorphéniramine, dextrométhorphan, diphénhydramine, famotidine, lopéramide, ranitidine, cimétidine, astémizole, terfénadine, carboxylate de terfénadine, certirizine, un sel pharmaceutiquement acceptable de ceux-ci ou un mélange, et où de préférence le produit pharmaceutique est acétaminophène, ibuprofène, lopéramide, famotidine ou aspirine.

9. Procédé de préparation d'une forme de dosage pharmaceutique à l'état comprimé, comprenant les étapes de:

   former au moins une particule enrobée comprenant au moins un produit pharmaceutique enrobé d'un enrobage donnant du goût;
   mélanger à sec ladite particule enrobée avec un carbohydrate compressible, désintégrable à l'eau et un liant et comprimer le mélange en une masse ayant une dureté suffisante pour forcer ledit carbohydrate à se désintégrer dans les 30 secondes après administration orale, pour ainsi permettre à ladite particule enrobée d'être avalée;
   où ladite forme de dosage pharmaceutique à l'état comprimé a une dureté dans la gamme d'environ 1,0 à environ 3,0 kp.

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(57) Abstract

An injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5, and an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is 9.5 - 11.5: (a): a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or salt thereof having antiulcer activity; (b): an aqueous solvent added with no nonaqueous solvent. The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

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SPECIFICATION

INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS

[TECHNICAL FIELD]

The present invention relates to an injection of 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, particularly sodium salt of omeprazole and to an injection kit thereof, which are used in clinical fields.

[BACKGROUND ART]

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds such as omeprazole or lansoprazole are potent antiulcer agents, and are used as pharmaceutical compositions for oral administration. Further, the injections thereof have recently developed.

As an injection of omeprazole, there has been known an injection prepared by dissolving sodium salt of omeprazole in sterilized water, filtering and lyophilizing the solution to give a lyophilized product, and then dissolving the lyophilized product in a mixture of polyethylene glycol 400 for injection, sodium dihydrogenphosphate and sterilized water (Japanese Patent Unexamined Publication No. 167587/1984).

Also, an injection prepared by dissolving a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compound having antiulcer activity such as lansoprazole in a mixture of (a) acid, and (b) at least one of ethanol, propylene glycol and polyethylene glycol

(Japanese Patent Unexamined Publication No. 138213/1990).

In general, the pH of injection is preferably about 4-8, and a pH above 9 has a probability of causing hemolysis and local irritation.

In the case of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt which may be hereinafter referred to as "benzimidazole compound or salt thereof" represented by sodium salt of omepazole, it shows a solubility of the level permitting formulation into preparation, in water in an alkaline range of pH 9.5 or above, whereas it shows extremely low solubility in water at a pH of not more than 9, thus rendering formulation into preparation very difficult.

While the benzimidazole compound or salt thereof is stable in the alkaline range, it poses a problem in that its stability decreases with the lowering pHs.

For this reason, it has been employed in conventional injections of benzimidazole compound or salt thereof such as sodium salt of omeprazole to add an acid such as hydrochloric acid or sodium dihydrogenphosphate to the solution to keep the pH from neutral to weak basic, and to further add a nonaqueous solvent such as polyethylene glycol, ethanol or propylene glycol in order to obtain a certain level of solubility in such pH range.

Yet, these injections pose problems of local irritation and hemolysis caused by the nonaqueous solvent added to the solution for dissolution.

Accordingly, an object of the invention is to provide an injection of benzimidazole compound or salt thereof, particularly sodium salt of omeprazole causing less side-effects such as hemolysis, and less local irritation, which permits easy formulation.

[DISCLOSURE OF THE INVENTION]

As a result of the intensive study conducted by the inventors with the aim of achieving the aforementioned object, it has now been found that a product obtained by lyophilizing an alkaline aqueous solution of benzimidazole compound or salt thereof, and dissolving same in an aqueous solvent added with no nonaqueous solvent scarcely shows hemolytic property and local irritation, notwithstanding the high pH of from 9.5 to 11.5.

Accordingly, the present invention is:

(1) an injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, which has a pH of not less than 9.5 and not more than 11.5,

(2) an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;

(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt

thereof having antiulcer activity

(b) : an aqueous solvent added with no nonaqueous solvent.

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds having antiulcer activity which are the element constituting the present invention include, for example, the compounds described in Japanese Patent Unexamined Publication No. 62275/1977, Japanese Patent Unexamined Publication No. 1417/1979, Japanese Patent Unexamined Publication No. 53406/1982, Japanese Patent Unexamined Publication No. 135881/1983, Japanese Patent Unexamined Publication No. 192880/1983, Japanese Patent Unexamined Publication No. 181277/1984 or Japanese Patent Unexamined Publication No. 50978/1986, and omeprazole [chemical name: 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole] and lansoprazole [chemical name: 2- {2-[(3-methyl-4-(2,2,2-trifluoroethoxy)]-pyridylmethylsulfinyl} -benzimidazole] are exemplified.

As the salts of said benzimidazole compounds, for example, salts of alkaline metal such as sodium salt or potassium salt or salts of alkaline earth metal such as calcium salt or magnesium salt.

In view of the solubility, it is preferable for the present invention to use the salt of benzimidazole compound.

The injection of the present invention has a pH of not less than 9.5 and not more than 11.5, preferably not less than 10 and not more than 11. Where the pH is less than 9.5, the benzimidazole compound or salt thereof does not sufficiently

dissolve in an aqueous solvent and shows poor stability, while where it is more than 11.5, hemolytic property and local irritation become prominent.

According to the present invention, an injection of the benzimidazole compound or salt thereof can be prepared by dissolving the benzimidazole compound or salt thereof in water for injection, etc. along with a strong alkaline compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or L-arginine, to give an alkaline aqueous solution having a pH adjusted to not less than 10.5 and not more than 12.5, preferably not less than 11 and not more than 12. The alkaline aqueous solution may contain mannitol, glycine, sorbitol, inositol, etc. on demand for better forming of a lyophilized product.

The benzimidazole compound is contained in said alkaline aqueous solution in a proportion of 1-50 mg/ml, preferably 5-40 mg/ml on a free compound basis.

Then, this alkaline aqueous solution is filtered for sterilization, and charged in a vial by 0.5-10 ml. After nitrogen gas displacement to be conducted as necessary, the solution is lyophilized by a method known per se. The lyophilized product thus obtained is the (a): a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compounds or salt thereof having antiulcer activity to be contained in the injection kit of the present invention.

When in use, the injection of the present invention can be produced by dissolving the lyophilized product thus obtained in an aqueous solvent added with no nonaqueous solvent, such as physiological saline, aqueous solution of 5% glucose, or distilled water for injection. Said aqueous solvent corresponds to the (b) : an aqueous solvent added with no nonaqueous solvent to be contained in the injection kit of the present invention.

The injection of the present invention can be used, for example, in the form of drip infusion, intravenous injection, intramuscular injection, subcutaneous injection.

The concentration of benzimidazole compound in the injection of the present invention may vary depending upon the administration route, and generally ranges in a proportion of 0.05-10 mg/ml, preferably 0.1-5 mg/ml on a free compound basis.

The benzimidazole compound in the injection of the present invention is administered to an adult at 10-100 mg per day on a free compound basis in a single to three times divided doses, depending upon, for example, the symptoms of the patients.

[BEST MODE FOR CARRYING OUT OF THE INVENTION]

Experimental Example 1

Test preparation

1. Preparation obtained in Example 1 to be mentioned later

Test method

1. Hemolysis test

Hemolysis was evaluated by Akaishi method using whole blood

of rabbit. The result is given in Table 1.

2. Local irritation test

Local irritation was evaluated by the comparison of necrotic muscular tissue area at the injection site in 3 rabbits at 2 days after the administration of 1 ml of the test preparation by intramuscular injection, with that in the rabbits administered with 1 ml of physiological saline or 1 ml of a 1.7% acetic acid solution, respectively by intramuscular injection.

The results are summarized in Table 2.

Test results

Table 1

Test preparation	pH	Hemolysis
Ex. 1	10.5	not observed

Table 2

Test preparation	pH	Necrotic area (mm^2)
Ex. 1	10.5	63
1.7% acetic acid solution (positive comparison solution)	—	398
physiological saline (negative comparison solution)	—	31

(average of 3 rabbits)

The preparation of the present invention is desirable as an injection, since it does not cause hemolysis at all despite the high pH, and causes less local irritation.

Example 1

1N Sodium hydroxide (2.3 ml) is added to 21.3 g of sodium salt of omeprazole (20 g as omeprazole), and water for injection is added thereto to adjust the pH to 11.5 and the total amount to 1 kg.

After filtration for sterilization, this alkaline aqueous solution is charged in 10 ml vials by 2 g. A rubber plug is half driven in, and nitrogen displacement is performed. Lyophilization by a conventional method and dissolution of the lyophilized product obtained in 10 ml of physiological saline give an omeprazole injection [4 mg (free compound)/ml].

[INDUSTRIAL APPLICABILITY]

The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent such as polyethylene glycol to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. As a result, irritation and hemolysis caused by the nonaqueous solvent can be avoided. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

CLAIMS

1. An injection comprising a 2-[(2-pyridyl)methylsulfinyl]-benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5.

2. The injection of Claim 1, prepared by dissolving a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity in the aqueous solvent added with no nonaqueous solvent.

3. An injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;

(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity

(b) : an aqueous solvent added with no nonaqueous solvent.

4. The injection of Claim 1 or 2, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof is sodium salt of omeprazole.

5. The injection kit of Claim 3, wherein the 2-[(2-pyridyl)-methylsulfinyl]benzimidazole compound or the salt thereof is sodium salt of omeprazole.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 93/00998

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/44; A61K9/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 382 489 (TAKEDA) 16 August 1990 see claims see page 7, line 50 - line 52 see example 2 ---	1-5
A	EP,A,0 124 495 (AKTIEBOLAGET HÄSSLE) 7 November 1984 cited in the application see claims see page 6, line 6 - line 15 see page 7, line 31 - line 37 see page 8, line 1 - line 8 see example 13 ---	1-5
A	EP,A,0 356 143 (TAKEDA) 28 February 1990 cited in the application see claims -----	1-5

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

1

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 SEPTEMBER 1993	07.10.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

JP 9300998
SA 76470

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 29/09/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0382489	16-08-90	CA-A-	2009741	10-08-90
		JP-A-	3173817	29-07-91
		US-A-	5013743	07-05-91
EP-A-0124495	07-11-84	AU-B-	563842	23-07-87
		AU-A-	2525784	06-09-84
		CA-A-	1264751	23-01-90
		GB-A,B	2137616	10-10-84
		JP-C-	1651336	30-03-92
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		JP-A-	59167587	21-09-84
		SU-A-	1314953	30-05-87
		US-A-	4738974	19-04-88
EP-A-0356143	28-02-90	JP-A-	2138213	28-05-90
		US-A-	5223515	29-06-93

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

(19) Europäisches Patentamt
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(87) International publication number: **WO 94/02141 (03.02.1994 Gazette 1994/04)**

(54) INJECTION AND INJECTION KIT CONTAINING OMEPRAZOLE AND ITS ANALOGS

Injizierbares Arzneimittel und Satz, die Omoprazol oder verwandte Verbindungenenthalten

INJECTION ET TROUSSE D'INJECTION CONTENANT DE L'OMEPRAZOLE ET SES ANALOGUES

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **28.07.1992 JP 201203/92**

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(56) References cited:
EP-A- 0 124 495
EP-A- 0 356 143
EP-A- 0 382 489

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EP 0 652 751 B1

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Description

[TECHNICAL FIELD]

The present invention relates to an injection of 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity, particularly sodium salt of omeprazole and to an injection kit thereof, which are used in clinical fields.

[BACKGROUND ART]

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds such as omeprazole or lansoprazole are potent antiulcer agents, and are used as pharmaceutical compositions for oral administration. Further, the injections thereof have recently developed.

As an injection of omeprazole, there has been known an injection prepared by dissolving sodium salt of omeprazole in sterilized water, filtering and lyophilizing the solution to give a lyophilized product, and then dissolving the lyophilized product in a mixture of polyethylene glycol 400 for injection, sodium dihydrogenphosphate and sterilized water (Japanese Patent Unexamined Publication No. 167587/1984).

Also, an injection prepared by dissolving a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound having antiulcer activity such as lansoprazole in a mixture of (a) acid, and (b) at least one of ethanol, propylene glycol and polyethylene glycol (Japanese Patent Unexamined Publication No. 138213/1990).

In general, the pH of injection is preferably about 4-8, and a pH above 9 has a probability of causing hemolysis and local irritation.

In the case of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt which may be hereinafter referred to as "benzimidazole compound or salt thereof" represented by sodium salt of omepazole, it shows a solubility of the level permitting formulation into preparation, in water in an alkaline range of pH 9.5 or above, whereas it shows extremely low solubility in water at a pH of not more than 9, thus rendering formulation into preparation very difficult.

While the benzimidazole compound or salt thereof is stable in the alkaline range, it poses a problem in that its stability decreases with the lowering pHs.

For this reason, it has been employed in conventional injections of benzimidazole compound or salt thereof such as sodium salt of omeprazole to add an acid such as hydrochloric acid or sodium dihydrogenphosphate to the solution to keep the pH from neutral to weak basic, and to further add a nonaqueous solvent such as polyethylene glycol, ethanol or propylene glycol in order to obtain a certain level of solubility in such pH range.

Yet, these injections pose problems of local irritation and hemolysis caused by the nonaqueous solvent added to the solution for dissolution.

Accordingly, an object of the invention is to provide an injection of benzimidazole compound or salt thereof, particularly sodium salt of omeprazole causing less side-effects such as hemolysis, and less local irritation, which permits easy formulation.

[DISCLOSURE OF THE INVENTION]

As a result of the intensive study conducted by the inventors with the aim of achieving the aforementioned object, it has now been found that a product obtained by lyophilizing an alkaline aqueous solution of benzimidazole compound or salt thereof, and dissolving same in an aqueous solvent added with no nonaqueous solvent scarcely shows hemolytic property and local irritation, notwithstanding the high pH of from 9.5 to 11.5.

Accordingly, the present invention is:

(1) an injection comprising a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, which has a pH of not less than 9.5 and not more than 11.5,

(2) an injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;

(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity

(b) : an aqueous solvent added with no nonaqueous solvent.

The 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds having antiulcer activity which are the element constituting the present invention include, for example, the compounds described in Japanese Patent Unexamined Publica-

tion No. 62275/1977, Japanese Patent Unexamined Publication No. 1417/1979, Japanese Patent Unexamined Publication No. 53406/1982, Japanese Patent Unexamined Publication No. 135881/1983, Japanese Patent Unexamined Publication No. 192880/1983, Japanese Patent Unexamined Publication No. 181277/1984 or Japanese Patent Unexamined Publication No. 50978/1986, and omeprazole [chemical name: 2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole] and lansoprazole [chemical name: 2- {2-[(3-methyl-4-(2,2,2-trifluoroethoxy)]-pyridylmethylsulfinyl} - benzimidazole] are exemplified.

As the salts of said benzimidazole compounds, for example, salts of alkaline metal such as sodium salt or potassium salt or salts of alkaline earth metal such as calcium salt or magnesium salt.

In view of the solubility, it is preferable for the present invention to use the salt of benzimidazole compound.

The injection of the present invention has a pH of not less than 9.5 and not more than 11.5, preferably not less than 10 and not more than 11. Where the pH is less than 9.5, the benzimidazole compound or salt thereof does not sufficiently dissolve in an aqueous solvent and shows poor stability, while where it is more than 11.5, hemolytic property and local irritation become prominent.

According to the present invention, an injection of the benzimidazole compound or salt thereof can be prepared by dissolving the benzimidazole compound or salt thereof in water for injection, etc. along with a strong alkaline compound such as sodium hydroxide, potassium hydroxide, sodium carbonate or L-arginine, to give an alkaline aqueous solution having a pH adjusted to not less than 10.5 and not more than 12.5, preferably not less than 11 and not more than 12. The alkaline aqueous solution may contain mannitol, glycine, sorbitol, inositol, etc. on demand for better forming of a lyophilized product.

The benzimidazole compound is contained in said alkaline aqueous solution in a proportion of 1-50 mg/ml, preferably 5-40 mg/ml on a free compound basis.

Then, this alkaline aqueous solution is filtered for sterilization, and charged in a vial by 0.5-10 ml. After nitrogen gas displacement to be conducted as necessary, the solution is lyophilized by a method known per se. The lyophilized product thus obtained is the (a): a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compounds or salt thereof having antiulcer activity to be contained in the injection kit of the present invention.

When in use, the injection of the present invention can be produced by dissolving the lyophilized product thus obtained in an aqueous solvent added with no nonaqueous solvent, such as physiological saline, aqueous solution of 5% glucose, or distilled water for injection. Said aqueous solvent corresponds to the (b) : an aqueous solvent added with no nonaqueous solvent to be contained in the injection kit of the present invention.

The injection of the present invention can be used, for example, in the form of drip infusion, intravenous injection, intramuscular injection, subcutaneous injection.

The concentration of benzimidazole compound in the injection of the present invention may vary depending upon the administration route, and generally ranges in a proportion of 0.05-10 mg/ml, preferably 0.1-5 mg/ml on a free compound basis.

The benzimidazole compound in the injection of the present invention is administered to an adult at 10-100 mg per day on a free compound basis in a single to three times divided doses, depending upon, for example, the symptoms of the patients.

[BEST MODE FOR CARRYING OUT OF THE INVENTION]

Experimental Example 1

<u>Test preparation</u>

1. Preparation obtained in Example 1 to be mentioned later

<u>Test method</u>

1. Hemolysis test

Hemolysis was evaluated by Akaishi method using whole blood of rabbit. The result is given in Table 1.

2. Local irritation test

Local irritation was evaluated by the comparison of necrotic muscular tissue area at the injection site in 3 rabbits at 2 days after the administration of 1 ml of the test preparation by intramuscular injection, with that in the rabbits administered with 1 ml of physiological saline or 1 ml of a 1.7% acetic acid solution, respectively by intramuscular injection.

The results are summarized in Table 2.

Test results

Table 1

Test preparation	pH	Hemolysis
Ex. 1	10.5	not observed

Table 2

Test preparation	pH	Necrotic area (mm^2)
Ex. 1	10.5	63
1.7% acetic acid solution (positive comparison solution)	-	398
physiological saline (negative comparison solution)	-	31
(average of 3 rabbits)		

The preparation of the present invention is desirable as an injection, since it does not cause hemolysis at all despite the high pH, and causes less local irritation.

Example 1

1N Sodium hydroxide (2.3 ml) is added to 21.3 g of sodium salt of omeprazole (20 g as omeprazole), and water for injection is added thereto to adjust the pH to 11.5 and the total amount to 1 kg.

After filtration for sterilization, this alkaline aqueous solution is charged in 10 ml vials by 2 g. A rubber plug is half driven in, and nitrogen displacement is performed. Lyophilization by a conventional method and dissolution of the lyophilized product obtained in 10 ml of physiological saline give an omeprazole injection [4 mg (free compound)/ml].

[INDUSTRIAL APPLICABILITY]

The injection of the present invention is void of the necessity to lower pH so as to prevent hemolysis and local irritation, and to add a nonaqueous solvent such as polyethylene glycol to an aqueous solvent for dissolution so as to prevent concomitant degradation of dissolution property. As a result, irritation and hemolysis caused by the nonaqueous solvent can be avoided. Accordingly, the injection of the present invention can secure solubility sufficient for formulation into preparation and safety for the human body.

Claims

1. An injection comprising a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity and an aqueous solvent added with no nonaqueous solvent, wherein the pH of the injection is not less than 9.5 and not more than 11.5.

2. The injection of Claim 1, prepared by dissolving a lyophilized product of an alkaline aqueous solution of the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity in the aqueous solvent added with no nonaqueous solvent.

3. An injection kit comprising the following (a) and (b), wherein (a) and (b) are adjusted such that the pH upon dissolution of (a) in (b) is not less than 9.5 and not more than 11.5;

(a) : a lyophilized product of an alkaline aqueous solution of a 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof having antiulcer activity
(b) : an aqueous solvent added with no nonaqueous solvent.

4. The injection of Claim 1 or 2, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or a salt thereof is sodium salt of omeprazole.

5. The injection kit of Claim 3, wherein the 2-[(2-pyridyl)methylsulfinyl]benzimidazole compound or the salt thereof is sodium salt of omeprazole.

Patentansprüche

1. Injizierbares Mittel, das eine 2-[(2-Pyridyl)-methylsulfinyl]-benzimidazolverbindung oder ein Salz derselben mit Antiulcusaktivität und ein mit keinem nichtwäßrigen Lösungsmittel zugesetztes wäßriges Lösungsmittel umfaßt, wobei der pH-Wert des injizierbaren Mittels nicht niedriger als 9,5 und nicht höher als 11,5 ist.

2. Injizierbares Mittel nach Anspruch 1, hergestellt durch Auflösen eines lyophilisierten Produktes einer alkalischen wäßrigen Lösung der 2-[(2-Pyridyl)-methylsulfinyl]-benzimidazolverbindung oder eines Salzes derselben mit Antiulcusaktivität in dem mit keinem nichtwäßrigen Lösungsmittel zugesetzten wäßrigen Lösungsmittel.

3. Injektions-Kit mit den folgenden Bestandteilen (a) und (b), worin (a) und (b) derart eingestellt sind, daß der pH-Wert beim Auflösen von (a) in (b) nicht niedriger als 9,5 und nicht höher als 11,5 ist, wobei

(a) ein lyophilisiertes Produkt einer alkalischen wäßrigen Lösung einer 2-[(2-Pyridyl)-methylsulfinyl]-benzimidazolverbindung oder eines Salzes hiervon mit Antiulcusaktivität ist und

(b) eine mit keinem nichtwäßrigen Lösungsmittel zugesetztes wäßriges Lösungsmittel ist.

4. Injizierbares Mittel nach Anspruch 1 oder 2, worin die 2[(2-Pyridyl)-methylsulfinyl]-benzimidazolverbindung oder ein Salz derselben Natriumsalz von Omeprazol ist.

5. Injektions-Kit nach Anspruch 3, worin die 2-[(2-Pyridyl)-methylsulfinyl]-benzimidazolverbindung oder das Salz derselben Natriumsalz von Omeprazol ist.

Revendications

1. Injection comprenant un composé de 2-[(2-pyridyl)méthylsulfinyl] benzimidazole ou un sel de celui-ci ayant une activité anti-ulcéreuse et un solvant aqueux sans ajout de solvant non aqueux dans laquelle le pH de l'injection n'est pas inférieur à 9,5 et n'est pas supérieur 11.5.

2. Injection selon la revendication 1, préparée en dissolvant un produit lyophilisé d'une solution aqueuse alcaline d'un composé de 2-[(2-pyridyl)méthylsulfinyl] benzimidazole ou un sel de celui-ci ayant une activité anti-ulcéreuse dans le solvant aqueux sans ajout de solvant non aqueux.

3. Trousse d'injection comprenant les composés suivants (a) et (b), dans laquelle (a) et (b) sont ajustés de telle sorte que le pH lors de la dissolution de (a) dans (b) ne soit pas inférieur à 9,5 ni supérieur à 11,5;

(a) un produit lyophilisé d'une solution aqueuse alcaline d'un composé 2-[(2-pyridyl)méthylsulfinyl] benzimidazole ou un sel de celui-ci ayant une activité anti-ulcéreuse
(b) : un solvant aqueux sans ajout de solvant non aqueux.

4. Injection selon la revendication 1 ou 2, dans laquelle le composé 2-[(2-pyridyl)méthylsulfinyl] benzimidazole ou le sel de celui-ci est un sel de sodium d'oméprazole.

5. Trousse d'injection selon la revendication 3, dans laquelle le composé 2-[(2-pyridyl)méthylsulfinyl] benzimidazole ou le sel de celui-ci est un sel de sodium d'oméprazole.

(19) Europäisches Patentamt
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(87) International publication number:
WO 94/25070 (10.11.1994 Gazette 1994/25)

(54) **VETERINARY COMPOSITION CONTAINING A PROTON PUMP INHIBITOR**
TIERARZNEIMITTEL, DAS EINEN PROTONENPUMPENINHIBITOR ENTHÄLT
COMPOSITION VETERINAIRE CONTENANT UN INHIBITEUR DE POMPE A PROTONS

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Designated Extension States:
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EP-A- 0 519 365
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EP 0 696 921 B1

Description

Technical Field

[0001] The invention relates to an oral pharmaceutical composition comprising a proton pump inhibitor (PPI) and is designed for the treatment of gastric acid related diseases in animals.

Background of the Invention

[0002] Proton pump inhibitors are potent inhibitors of gastric acid secretion and are used for the treatment of gastric acid related diseases in humans, such as for instance gastric and duodenal ulcers. These substances are susceptible to degradation/transformation in acid reacting and neutral media. Pharmaceutical formulations for oral administration to humans are preferably enteric-coated. These formulations are sensitive to moisture and must be stored in well-closed, tight containers during long-term storage.

[0003] Peptic ulcer diseases are common also in some animals, especially in horses and camels. Other animals of interest for treatment of peptic ulcer diseases are for example dolphins, sea-lions, llamas, dogs, cats and pigs. By gastro-endoscopic evaluation of horses, ulcers have been found in the squamous mucosa, the non glandular fundus, the glandular stomach and the duodenum. The aetiology of gastro-duodenal ulcers in the equine species is mainly unknown but stress appears to play an important role in some cases.

[0004] Anti-ulcer compounds such as for instance histamine-2-receptor antagonists have reportedly been administered several times a day to horses by oral or naso-gastric tubes. This procedure can be traumatic and may require light sedation of the horse. Trained persons are required for the administration.

[0005] Omeprazole and other proton pump inhibitors are potent inhibitors of gastric acid secretion in animals. They block the production of gastric acid by inhibition of H^+K^+-ATPase, the enzyme responsible for the production of hydrogen ions in the parietal cells. The proton pump inhibitors cause profound acid suppression and unlike most other anti-ulcer compounds such as for instance the H_2-blockers, omeprazole can be given once daily. According to the present invention enteric-coated beads containing omeprazole in a gel formulation can easily be applied onto the dorsal part of the tongue of the horse during field conditions and is well accepted by the horses.

[0006] Such a moist gel comprising enteric-coated beads of proton pump inhibitors is not stable during long-term storage at room temperature and must be prepared ex tempore. To-day there exist no such formulation on the market.

[0007] Omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is disclosed in European patent no 5129 as a potent inhibitor of gastric acid secretion.

[0008] Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole, is disclosed in European patent no 174 726 as a potent inhibitor of gastric acid secretion.

[0009] Pantoprazole is disclosed in European patent no 166 287 as a potent inhibitor of gastric acid secretion.

[0010] Leminoprazole is disclosed in UK patent no 2 163 747.

[0011] An oral pharmaceutical formulation comprising omeprazole is disclosed in European patent application 496437. The formulation contains a core material comprising omeprazole together with an alkaline reacting compound, or an alkaline salt of omeprazole optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers and an outer layer which is an enteric coating. The formulation is claimed to be stable against discoloration.

[0012] European patent application 519365 describes an oral pharmaceutical formulation comprising pantoprazole in the form of enteric coated pellets or tablets.

[0013] Neither EP 496437 nor EP 519365 suggests enteric coated pellets incorporated into a gel.

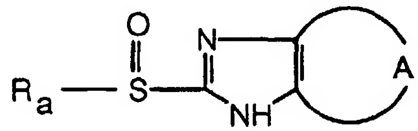
[0014] WO8806893 describes an oral composition which is adapted to be dispersed in an aqueous carrier prior to administration. Particles comprising the active drug substance will obtain a smooth surface, thereby masking uneven surfaces by providing a viscous medium around the particles when dispersed in the aqueous carrier and prevent adhesion of the particles to the wall of a container.

Detailed description of the invention

[0015] The object of the present invention is to provide oral pharmaceutical compositions for easy administration to horses and other animals. The proton pump inhibitor is in the form of dry particles, such as beads or tablets, which are coated with one or more coatings one of which is an enteric-coating. The beads or tablets can be prepared by compaction, crystallisation, applying a solution or suspension of the proton pump inhibitor onto inert cores, extrusion and spheronisation or similar processes. The enteric-coated beads or tablets are mixed with dry gelling agent(s), such as for instance xanthan gum, guar gum, locust bean gum, tragacanth, modified cellulose derivatives or similar gel forming compounds. When water is added to this mixture a paste-like gel is formed. The gel is for example applied dorsally at

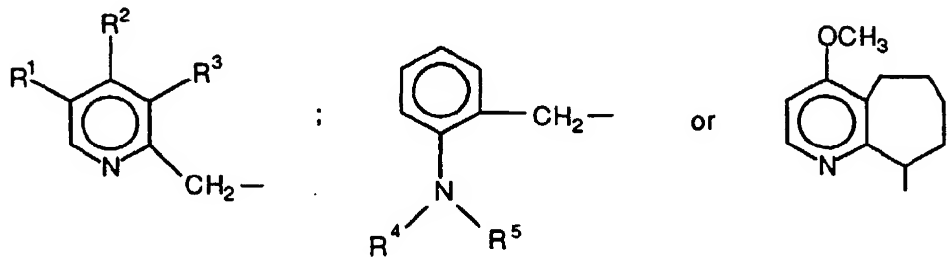
the tongue of the animal such as a horse with a suitable applicator.

[0016] Proton pump inhibitors used in the compositions of the invention are compounds of the general formula I

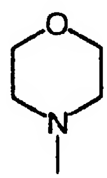


I

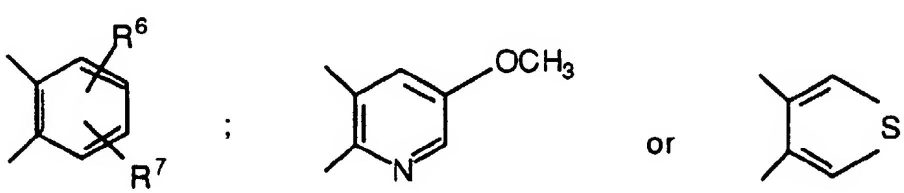
wherein R_a is



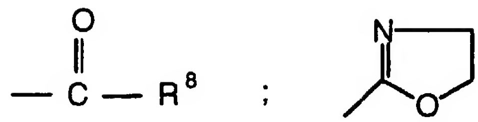
R^1 and R^3 are independently selected from hydrogen, lower alkyl, lower alkoxy and halogen, R^2 is selected from hydrogen, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower fluoralkoxy and



R^4 and R^5 are independently selected from lower alkyl,
A is



R^6 and R^7 are independently selected from hydrogen, lower alkyl, lower alkoxy, lower fluoroalkoxy, lower fluoroalkyl, halogen,

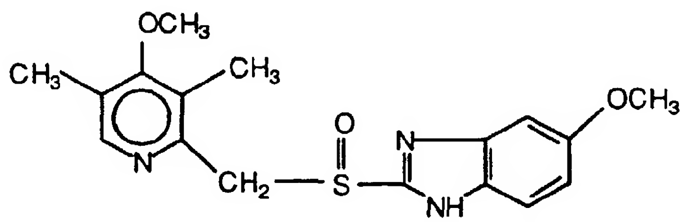


wherein R^8 is lower alkyl or lower alkoxy.

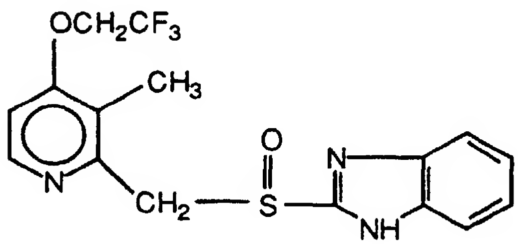
[0017] Lower alkyl in the present invention means an alkyl group having 1-5 carbon atoms.

[0018] Lower alkoxy in the present invention means an alkoxy group having 1-5 carbon atoms.

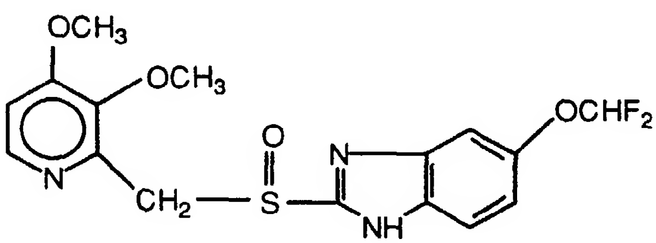
[0019] Examples of proton pump inhibitors according to formula I are



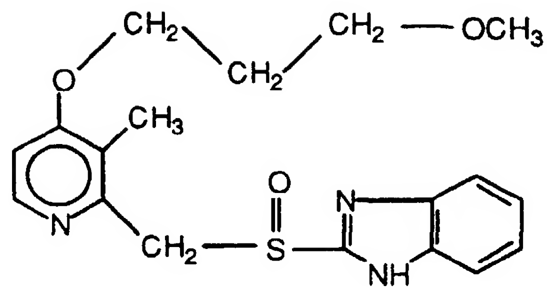
Omeprazole



Lanzoprazole



Pantoprazole



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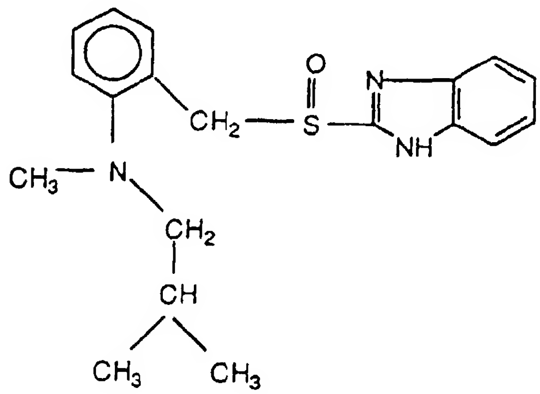
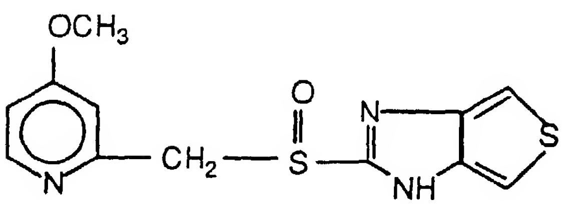


Leminoprazole



S— 4216 .

[0020] The proton pump inhibitors used in the compositions of the invention may be used in neutral form or in the form of a basic salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+}, or K^{+} salts, preferably the Mg^{2+} or Na^{+} salts. Further where applicable, a compound listed above may be used in racemic form or in the form of a substantially pure enantiomer.

[0021] In one embodiment of the invention the enteric-coated particles are mixed with suitable substances, such as for instance suitable inorganic or organic water soluble salts of potassium, calcium, magnesium or aluminium. When a water solution of a suitable polymeric compound or compounds, such as for instance kappa-carrageenan, pectin, anionic polymers known to give gels with positively charged metal ions, or similar compounds, is added to the mixture a paste-like gel is formed through the interaction of the ions with the polymers.

[0022] In another embodiment of the invention the enteric-coated particles are mixed with suitable constituents. When a low-viscous solution of a temperature-sensitive polymer, such as for instance ethylhydroxyethylcellulose (EHEC) or polyethylenepolypropylene glycols or similar substances, is added and the system is warmed to temperatures of 33-35°C or higher a viscous paste-like gel is formed.

[0023] In still another embodiment of the invention the enteric-coated particles are mixed with suitable substances in the form of gelforming agents, such as dry gelling agent. As gelforming agents can be used for example acacia,

agar, alginic acid, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose or other similar cellulose derivatives, fucoidan, xanthan gum, furcellaran, laminaran or similar gelforming agents.

[0024] In a preferred embodiment of the invention the proton pump inhibitor is omeprazole.

[0025] The amount of the different components of the composition can vary and will depend on various factors such as for example the individual requirement of the animal treated.

[0026] The amount of gelforming agent can vary but is within the range 0.02-20% by weight calculated on the amount of wet gel, preferably in the range of 0.2-20% and especially 0.5-5% by weight.

[0027] The amount of active substance, i.e. the enteric-coated particles, depends on the individual dosages for the animal. For example the amount of enteric-coated particles is usually in the range of 0.1-20 grams, preferably 0.2-10 grams per dosage for horses. The total volume of the final gel given to horses is in the range of 5-50 ml.

[0028] Other suitable substances which may be incorporated in the composition are flavouring substances known in the pharmaceutical field.

[0029] The suitable substances may be added to the enteric-coated proton pump inhibitor particles by mixing the different substances with the enteric-coated particles to a mixture or an ordered mixture. An ordered mixture may be produced for example by particle adhesion or coating processes.

[0030] The mixtures of enteric-coated proton pump inhibitor particles and the suitable constituents are dried before or after mixing to a moisture level where the proton pump inhibitor has a good long-term stability. The mixture is preferably dispensed into a tight applicator preferably in the form of a syringe.

[0031] The mixture of the enteric-coated proton pump inhibitor beads or tablets and other constituents can also comprise a suitable pH-buffering substance which will improve the functional stability of the formulation during its transport through the oesophagus and stomach before it reaches the small intestine where the proton pump inhibitor is dissolved and absorbed. Suitable buffering substances are citric acid, tartaric acid, succinic acid, malic acid, lactic acid, benzoic acid, sorbic acid and ascorbic acid and other substances. Such substances will decrease the pH-value of the gel produced to a value below 5.5, thus protecting the enteric coating of the beads or tablets.

[0032] Further the mixture of the enteric coated proton pump inhibitor particles and suitable constituents may also comprise inert particles, such as inert beads to facilitate the mixing of the different constituents with the enteric-coated particles. Such inert beads are for example beads of coated suger or any other kind of beads not harmful to the animal.

[0033] Enteric coated beads or tablets can be prepared by conventional methods. Enteric-coated pellets of omeprazole can for instance be prepared as described in the US Patent No. 4,786,505 (=EP 247983). Such enteric coated pellets or beads of omeprazole are preferably coated with at least two coatings one of which is an isolation coating/ subcoat and the other is an enteric coating.

[0034] The preparation of a stable pharmaceutical composition according to the invention is performed by incorporating a proton pump inhibitor in the form of beads or tablets, which are coated with one ore more coatings one of which is an enteric-coating, into a paste-like gel.

[0035] More particular, the preparation of a formulation in the form of a paste-like gel is performed by either I) mixing the coated particles of the proton pump inhibitor with a dry gelling agent and optionally a pH-buffering system protecting the coated particles whereafter water is added ex tempore, just prior to administration to the animal, or II) mixing the coated particles with a potassium or calcium ion containing salt and optionally a pH-buffering system and thereafter ex tempore, just prior to administration to the animal, with a low-viscous water solution of a gelling agent such as a polymer compound or compounds or by III) mixing the coated particles ex tempore, just prior to administration to the animal, with a low-viscous solution of a gelling agent in the form of temperature-sensitive polymer and optionally with a pH-buffering system and then subjecting the mixture to gentle heating.

Examples

[0036] The omeprazole enteric-coated pellets in the examples below are prepared according to example 2 of US-A 4,786,505 (=EP 247983).

Example 1

[0037]

Omeprazole enteric-coated pellets (corresponding to about 600 mg of omeprazole)	7 g
Xanthan gum are mixed in a syringe.	0.3 g

[0038] When 10 ml of water are added a viscous gel is formed.

Example 2

[0039]

Omeprazole enteric-coated pellets	7 g
Xanthan gum	0.3 g
Citric acid are mixed in a syringe.	60 mg

[0040] When 10 ml of water are added a viscous gel is formed.

Example 3

[0041]

Omeprazole enteric-coated pellets	7 g
Potassium chloride are mixed in a syringe.	30 mg

[0042] When 10 ml of a 1% solution of kappa-carrageenan are added a viscous gel is formed.

Example 4

[0043]

Omeprazole enteric-coated pellets are dispensed into a syringe.	7 g

[0044] When 10 ml of a solution of EHEC (ethylhydroxyethylcellulose) 1.25% and sodium lauryl sulphate 0.1% are added and warmed to 35°C a viscous gel is formed.

Example 5

[0045]

Lansoprazole enteric-coated pellets (prepared according to examples 1 and 2 of EP 277 741, hereby incorporated by reference) (corresponding to lansoprazole ~900 mg)	10 g
Xanthan gum	0.45 g
Citric acid	80 mg

[0046] When 15 ml of water are added a viscous gel is formed.

Example 6

[0047]

Pantoprazole enteric-coated pellets (prepared according to example 2 of EP 519 365, hereby incorporated by reference) (corresponding to pantoprazole ~1200 mg)	7 g
Xanthan gum	0.3 g
Citric acid	50 mg

[0048] When 10 ml of water are added a viscous gel is formed.
[0049] The best mode of carrying out the invention known at present is to use the composition described in Example 2.

Claims

1. A pharmaceutical composition for oral administration to animals characterized in that it comprises a proton pump

inhibitor in the form of beads or tablets, which are coated with one or more coatings one of which is an enteric-coating, and that the proton pump inhibitor in the form of beads or tablets is incorporated into a paste-like gel.

2. A pharmaceutical composition according to claim 1, characterized in that the beads or tablets are coated with at least two coatings one of which is a subcoat and the other is an enteric coating.

3. A pharmaceutical composition according to any of claims 1-2, characterized in that the pharmaceutical composition is intended for oral administration to horses.

4. A pharmaceutical composition according to any of claims 1-2, characterized in that the composition comprises components which are dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry constituents, which components on addition of water or a water solution gives a paste-like gel.

5. A pharmaceutical composition according to any of claims 1-2 characterized in that it comprises components which are dry enteric-coated beads or tablets of a proton pump inhibitor, dry gelling agent(s) and optionally pH-buffering and/or flavouring substances which components by the addition of water gives a paste-like gel.

6. A pharmaceutical composition according to any of claims 1-2 characterized in that the dry enteric-coated beads or tablets of a proton pump inhibitor, dry gelling agent(s) and optionally pH-buffering and/or flavouring substances are mixed to a dry mixture before the addition of water or a water solution.

7. A pharmaceutical composition according to claim 6 characterized in that the mixture is an ordered mixture.

8. A pharmaceutical composition according to any of claims 1-2 characterized in that it comprises a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, a water soluble, organic or inorganic salt of potassium, calcium, magnesium or aluminium and optionally pH-buffering and/or flavouring substances, and a second group of components which is a water solution of a gelling agent, which groups of components when mixed give a paste-like gel.

9. A pharmaceutical composition according to any of claims 1-2 characterized in that it comprises a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry pH-buffering and/or flavouring substances, and a second group of components which is a water solution of a temperature sensitive gelling agent, which groups of components when mixed and subjected to gentle heating give a paste-like gel.

10. A pharmaceutical composition according to claim 1 characterized in that the proton pump inhibitor is omeprazole.

11. A pharmaceutical composition according to claim 1 characterized in that the proton pump inhibitor is lansoprazole.

12. A pharmaceutical composition according to claim 1 characterized in that the proton pump inhibitor is pantoprazole.

13. A pharmaceutical composition according to claim 1 characterized in that the proton pump inhibitor is leminoprazole.

14. A stable pharmaceutical composition for oral administration to animals in the form of a kit comprising dry enteric coated beads of tablets of a proton pump inhibitor and dry consituents, which components on addition of water or a water solution give a paste-like gel.

15. A stable pharmaceutical composition for oral administration to animals in the form of a kit comprising a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, a water soluble, organic or inorganic salt of potassium, calcium, magnesium or aluminium and optionally pH-buffering and/or flavouring substances, and a second group of components which is dry gelling agent(s), which groups of components when mixed in the presence of water give a paste-like gel.

16. A stable pharmaceutical composition for oral administration to animals in the form of a kit comprising a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry pH-buffering and/or flavouring substances, and a second group of components which are temperature sensitive gelling agent(s), which groups of components when mixed in the presence of water and subjected to gentle heating give a paste-like gel.

17. A pharmaceutical composition according to any of the claims 1, 14, 15 or 16 characterized in that the composition in its entirety or parts thereof is dispensed into an applicator in the form of a syringe.

18. A process for the preparation of a pharmaceutical composition according to claim 1, characterized by incorporating a proton pump inhibitor in the form of beads which are coated with one or more coatings one of which is an enteric-coating into a paste-like gel.

19. Use of a composition according to any of claims 1, 14, 15 or 16 in the preparation of an active dosage form for the treatment of gastric acid related diseases in animals.

Patentansprüche

1. Pharmazeutische Zusammensetzung zur oralen Verabreichung an Tiere, enthaltend einen Protonenpumpenhemmer in Form von mit einem oder mehreren Überzügen - von denen einer magensaftresistent ist - beschichteten Perlen oder Tabletten, dadurch gekennzeichnet, daß der Protonenpumpenhemmer in Form von Perlen oder Tabletten in ein pastenartiges Gel eingearbeitet ist.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Perlen oder Tabletten mit wenigstens zwei Überzügen beschichtet sind, von denen der eine eine Unterschicht und der andere ein magensaftresistenter Überzug ist.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die pharmazeutische Zusammensetzung zur oralen Verabreichung an Pferde gedacht ist.

4. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Zusammensetzung Komponenten enthält, bei denen es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers handelt, gegebenenfalls gemischt mit trockenen Inhaltsstoffen, wobei die Komponenten bei Zugabe von Wasser oder einer wäßrigen Lösung ein pastenartiges Gel bilden.

5. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß sie Komponenten enthält, bei denen es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers, trockene(s) Geliermittel und gegebenenfalls Puffer- und/oder Geschmacksstoffe handelt und die bei Zugabe von Wasser ein pastenartiges Gel bilden.

6. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die trockenen, magensaftresistent beschichteten Perlen oder Tabletten eines Protonenpumpenhemmers, das/die trockene(n) Geliermittel und gegebenenfalls Puffer- und/oder Geschmacksstoffe vor der Zugabe von Wasser oder einer wäßrigen Lösung zu einer trockenen Mischung vermischt werden.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, dadurch gekennzeichnet, daß es sich bei der Mischung um eine geordnete Mischung handelt.

8. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß sie eine erste Gruppe von Komponenten, bei denen es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers, ein wasserlösliches organisches oder anorganisches Kalium-, Calcium-, Magnesium- oder Aluminiumsalz und gegebenenfalls Puffer- und/oder Geschmacksstoffe handelt, und eine zweite Gruppe von Komponenten, bei der es sich um eine wäßrige Lösung eines Geliermittels handelt, enthält, wobei die Komponentengruppen beim Mischen ein pastenartiges Gel ergeben.

9. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß sie eine erste Gruppe von Komponenten, bei der es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers, gegebenenfalls gemischt mit trockenen Puffer- und/oder Geschmacksstoffen, handelt, und eine zweite Gruppe von Komponenten, bei der es sich um eine wäßrige Lösung eines temperaturempfindlichen Geliermittels handelt, enthält, wobei die Komponentengruppen beim Mischen und leichten Erwärmen ein pastenartiges Gel ergeben.

10. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Protonen-

pumpenhemmer um Omeprazol handelt.

11. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Protonenpumpenhemmer um Lansoprazol handelt.

12. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Protonenpumpenhemmer um Pantoprazol handelt.

13. Pharmazeutische Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß es sich bei dem Protonenpumpenhemmer um Leminoprazol handelt.

14. Stabile pharmazeutische Zusammensetzung zur oralen Verabreichung an Tiere in Form eines Kits, enthaltend trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers und trockene Inhaltsstoffe, wobei die Komponenten bei Zugabe von Wasser oder einer wäßrigen Lösung ein pastenartiges Gel ergeben.

15. Stabile pharmazeutische Zusammensetzung zur oralen Verabreichung an Tiere in Form eines Kits, enthaltend eine erste Gruppe von Komponenten, bei der es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers, ein wasserlösliches organisches oder anorganisches Kalium-, Calcium-, Magnesium- oder Aluminiumsalz und gegebenenfalls Puffer- und/oder Geschmacksstoffe handelt, und eine zweite Gruppe von Komponenten, bei der es sich um trockene(s) Geliermittel handelt, wobei die Komponentengruppen beim Mischen in Gegenwart von Wasser ein pastenartiges Gel ergeben.

16. Stabile pharmazeutische Zusammensetzung zur oralen Verabreichung an Tiere in Form eines Kits, enthaltend eine erste Gruppe von Komponenten, bei der es sich um trockene, magensaftresistent beschichtete Perlen oder Tabletten eines Protonenpumpenhemmers, gegebenenfalls gemischt mit trockenen Puffer- und/oder Geschmacksstoffen, handelt, und eine zweite Gruppe von Komponenten, bei denen es sich temperaturempfindliche (s) Geliermittel handelt, wobei die Komponentengruppen beim Mischen in Gegenwart von Wasser und leichten Erwärmen ein pastenartiges Gel ergeben.

17. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1, 14, 15 oder 16, dadurch gekennzeichnet, daß die gesamte Zusammensetzung oder Teile davon in einen Applikator in Form einer Spritze dispensiert wird.

18. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß ein Protonenpumpenhemmer in Form von mit einem oder mehreren Überzügen - von denen einer magensaftresistent ist - beschichteten Perlen in ein pastenartiges Gel eingearbeitet wird.

19. Verwendung einer Zusammensetzung nach einem der Ansprüche 1, 14, 15 oder 16 zur Herstellung einer wirksamen Dosierungsform zur Behandlung von mit Magensäure verbundenen Erkrankungen bei Tieren.

Revendications

1. Composition pharmaceutique pour l'administration orale aux animaux, caractérisée en ce qu'elle comprend un inhibiteur de la pompe à protons sous forme de billes ou de comprimés qui sont enduits avec un ou plusieurs enrobages dont un est un enrobage à délitage entérique, caractérisée en ce que l'inhibiteur de la pompe à protons sous forme de billes ou de comprimés est incorporé dans un gel de type pâte.

2. Composition pharmaceutique selon la revendication 1, caractérisée en ce que les billes ou les comprimés sont enduits avec au moins deux enrobages dont l'un est une sous-couche et l'autre est un enrobage à délitage entérique.

3. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce que la composition pharmaceutique est destinée à l'administration orale aux chevaux.

4. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce que la composition comprend des composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, facultativement mélangés avec des constituants secs, composants qui, lors de l'addition d'eau

ou d'une solution aqueuse, donnent un gel de type pâte.

5. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce qu'elle comprend des composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, d'un ou de plusieurs agents gélifiants secs et facultativement de substances de tamponnement du pH et/ou de substances aromatisantes, composants qui, par addition d'eau, donnent un gel de type pâte.

6. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce que les billes ou les comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, d'un ou de plusieurs agents gélifiants secs et facultativement de substances de tamponnement du pH et/ou de substances aromatisantes, sont mélangés en un mélange sec avant l'addition d'eau ou d'une solution aqueuse.

7. Composition pharmaceutique selon la revendication 6, caractérisée en ce que le mélange est un mélange ordonné.

8. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce qu'elle comprend un premier groupe de composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, d'un sel organique ou inorganique soluble dans l'eau de potassium, de calcium, de magnésium ou d'aluminium et facultativement de substances de tamponnement du pH et/ou de substances aromatisantes, et un second groupe de composants qui sont une solution aqueuse d'un agent gélifiant, groupes de composants qui, mélangés, donnent un gel de type pâte.

9. Composition pharmaceutique selon l'une quelconque des revendications 1-2, caractérisée en ce qu'elle comprend un premier groupe de composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, facultativement mélangés à des substances sèches de tamponnement du pH et/ou des substances sèches aromatisantes, et un second groupe de composants qui sont une solution aqueuse d'un agent gélifiant sensible à la température, groupes de composants qui, mélangés et soumis à un léger chauffage, donnent un gel de type pâte.

10. Composition pharmaceutique selon la revendication 1, caractérisée en ce que l'inhibiteur de la pompe à protons est l'oméprazole.

11. Composition pharmaceutique selon la revendication 1, caractérisée en ce que l'inhibiteur de la pompe à protons est le lansoprazole.

12. Composition pharmaceutique selon la revendication 1, caractérisée en ce que l'inhibiteur de la pompe à protons est le pantoprazole.

13. Composition pharmaceutique selon la revendication 1, caractérisée en ce que l'inhibiteur de la pompe à protons est le léminoprazole.

14. Composition pharmaceutique stable pour l'administration orale aux animaux sous forme d'une trousse comprenant des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons et de constituants secs, composants qui, lors de l'addition d'eau ou d'une solution aqueuse, donnent un gel de type pâte.

15. Composition pharmaceutique stable pour l'administration orale aux animaux sous forme d'une trousse comprenant un premier groupe de composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, d'un sel organique ou inorganique soluble dans l'eau de potassium, de calcium, de magnésium ou d'aluminium et facultativement de substances de tamponnement du pH et/ou des substances aromatisantes, et un second groupe de composants qui sont un ou plusieurs agents gélifiants secs, groupes de composants qui, mélangés en présence d'eau, donnent un gel de type pâte.

16. Composition pharmaceutique stable pour l'administration orale aux animaux sous forme d'une trousse comprenant un premier groupe de composants qui sont des billes ou des comprimés secs à délitage entérique d'un inhibiteur de la pompe à protons, facultativement mélangés à des substances sèches de tamponnement du pH et/ou des substances sèches aromatisantes, et un second groupe de composants qui sont un ou des agents gélifiants sensibles à la température, groupes de composants qui, mélangés en présence d'eau et soumis à un léger chauffage, donnent un gel de type pâte.

17. Composition pharmaceutique selon l'une quelconque des revendications 1, 14, 15 ou 16 caractérisée en ce que la composition dans son entièreté ou en partie est distribuée dans un applicateur sous forme de seringue.

18. Procédé pour la préparation d'une composition pharmaceutique selon la revendication 1, caractérisé par l'incorporation d'un inhibiteur de la pompe à protons sous forme de billes qui sont enduites avec un ou plusieurs enrobages dont un est un enrobage à délitage entérique dans un gel de type pâte.

19. Utilisation d'une composition selon l'une quelconque des revendications 1, 14, 15 ou 16 dans la préparation d'une forme active de dosage pour le traitement de maladies liées à l'acide gastrique chez des animaux.

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(54) STABILIZED COMPOSITIONS CONTAINING BENZIMIDAZOLE-TYPE COMPOUNDS

(57) Chemically stabilized preparations of benzimidazole-type compounds. These compositions comprise the benzimidazole-type compounds or alkali metal salts thereof together with at least one substance selected from among sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.

EP 1 004 305 A1

Description

Field of the Invention

[0001] The present invention relates to pharmaceutical preparations of the solid dosage form for internal use comprising benzimidazole type compounds or alkali metal salts thereof.

Prior Art

[0002] A benzimidazole type compound or an alkali metal salt thereof has a strong inhibitory action on the so-called proton pump, and it is widely used as a therapeutic agent for stomach ulcer, duodenal ulcer etc., by inhibiting gastric acid secretion. On the other hand, the benzimidazole type compound is chemically very unstable, so various measures have been invented for pharmaceutical manufacturing thereof. For example, JP-A 62-277322 discloses a process for producing a stabilized pharmaceutical composition comprising a basic inorganic salt of magnesium and/or calcium incorporated into a benzimidazole type compound, and JP-A 62-258320 discloses an oral pharmaceutical preparation prepared by incorporating an alkali compound into the portion of a core containing a benzimidazole type compound, then coating it with fillers for tablets soluble in water or rapidly degradable with water or with a polymeric and water-soluble film-forming compound, and further coating it with an enteric coating.

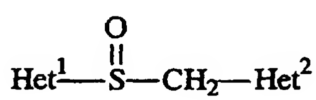
[0003] However, the stability of such pharmaceutical preparations is still insufficient even by the prior art described above, so there is demand for further improvements. That is, the object of the present invention is to further stabilize a pharmaceutical preparation of the solid dosage form for internal use comprising a benzimidazole type compound.

Disclosure of the Invention

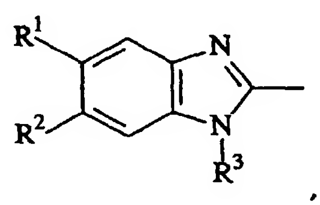
[0004] The present invention relates to a composition comprising at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by the structural formula (formula 1) below or an alkali metal salt thereof.

Formula 1

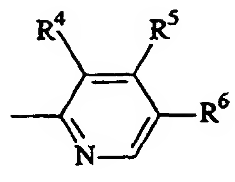
[0005]



[0006] In the formula 1, Het^1 is



Het^2 is



R^1 and R^2 are the same as or different from each other and are selected from a hydrogen, a methoxy and a difluoromethoxy, R^3 is selected from a hydrogen and a sodium, R^4, R^5 and R^6 are the same as or different from each other and are selected from a hydrogen, a methyl, a methoxy, a methoxypropoxy and a trifluoroethoxy.

[0007] Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1 or an alkali metal salt thereof, is coated with an enteric coating.

[0008] Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1 or an alkali metal salt thereof, coated with an intermediate coating and further with an enteric coating.

[0009] The present invention further relates to a pharmaceutical preparation comprising a core which comprises at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula loran alkali metal salt thereof, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

[0010] The present invention relates to a pharmaceutical composition comprising (A) benzimidazole type compound represented by formula 1 or an alkali metal salt thereof and (B) at least one substance selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.

[0011] Further, the present invention relates to a pharmaceutical preparation comprising a core consisting of the composition described above and an enteric coating. The pharmaceutical preparation may comprise an intermediate coating, an enteric coating and a moisture resistant coating besides the core.

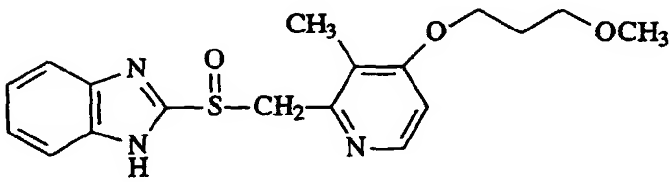
[0012] The moisture resistant coating is effective not only for the benzimidazole type compound but also for a drug whose decomposition is observed to be accelerated both in the presence of water and upon contact with gastric acid. That is, the present invention relates to a pharmaceutical preparation comprising a core coated with an enteric coating and further with a moisture resistant coating, said core comprising a drug incorporated into it and the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid.

[0013] Further, the present invention relates to a pharmaceutical preparation comprising a core coated with an intermediates coating, further with an enteric coating and then with a moisture resistant coating, said core comprising a drug incorporated into it and the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid.

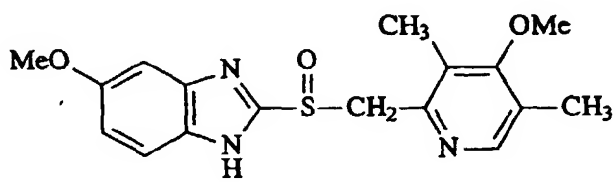
[0014] In the present invention, the benzimidazole type compounds or alkali metal salts thereof include e.g. rabeprazole, omeprazole, pantoprazole and lansoprazole, or sodium or potassium salts thereof. The structural formulae of these compounds are shown in formula 3.

Formula 3

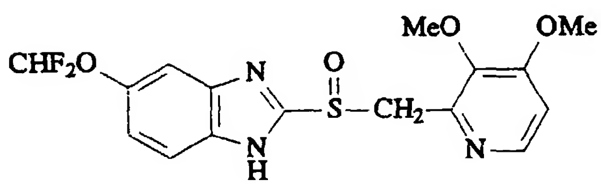
[0015]



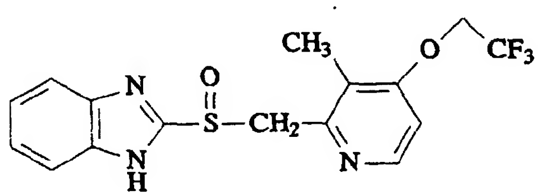
Rabeprazole



Omeprazole



Pantoprazole



Lansoprazole

[0016] Hereinafter, the benzimidazole type compound or an alkali metal salt thereof is collectively referred to as benzimidazole type compound.

[0017] The benzimidazole type compound in the present invention can be produced in a known method. For example, the compound can be produced by any methods disclosed in JP-A 52-62275, JP-A 54-141783, JP-A 1-6270 etc.

[0018] Sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide and hydroxypropyl cellulose in the present invention are mentioned in the Japanese Pharmacopoeia, and these are commercially available and easily obtainable. Aminoalkyl methaacrylate copolymer E, which is mentioned in the standards of non-medicines in the Japanese Pharmacopoeia, can be easily obtained. Further, crospovidone is a substance mentioned in the standards of pharmaceutical additives, and its commercial products of various grades with varying particle diameters are easily available, and their particle diameters can be regulated as necessary by a grinding device such as hammer mill.

[0019] The blending ratio of the benzimidazole type compound to at least one selected from sodium carbonate,

potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymner E, arginine aspartate, hydroxypropyl cellulose and crospovidone is 0.01 to 20 parts by weight, preferably 0.01 to 10 parts by weight, more preferably 0.1 to 10 parts by weight in total, to 1 part by weight of the benzimidazole type compound. In the present invention, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone can be used alone or 2 or more of these additives can be used in combination. Among these, it is effective to incorporate sodium hydroxide, potassium hydroxide and/or sodium carbonate into the benzimidazole type compound and it is more effective to incorporate 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate into the benzimidazole type compound. The blending ratio of a combination of these additives is 0.01 to 20 parts by weight to 1 part by weight of the benzimidazole type compound, and preferably the ratio of crospovidone is 0.5 to 5 parts by weight, and the ratio of sodium hydroxide, potassium hydroxide and/or sodium carbonate is 0.01 to 2 parts by weight.

[0020] The benzimidazole type compound when decomposed during storage under heating and humid conditions is observed to undergo significant coloring changes in particular. The composition and/or the pharmaceutical preparation of the invention comprising the above-described various additives incorporated into it possesses the particularly outstanding effect of not only improving the stability of the ingredients but also inhibiting the coloring changes.

[0021] Conventionally used excipients such as lactose and mannitol can be used to prepare a pharmaceutical preparation by use of the invented composition comprising the benzimidazole type compound and at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated thereto. Preferably, hydroxypropyl cellulose is used as a binder and crospovidone is used as a disintegrating agent.

[0022] It is known that crospovidone used generally as a disintegrating agent, when finely ground, can reduce the disintegrating force and swelling force inherent in the original disintegrating agent. Finely ground crospovidone having small particle diameters is used as a stabilizer for the benzimidazole type compound in the present invention, and it can be added in a larger amount than the amount of a usual disintegrating agent (usually 10 % or less). The average particle diameter of crospovidone is several μm to 50 μm, more preferably 4 μm to 50 μm.

[0023] Accordingly, the crospovidone used in the composition or in the pharmaceutical preparation according to the present invention is preferably crospovidone having small average particle diameters of several μm to 50 μm, preferably 4 μm to 50 μm. As a matter of course, finely ground crospovidone and usual crospovidone may be used in combination.

[0024] The crospovidone, though varying depending on manufacturer and lot number, often contains a slight amount of peroxides as impurities. The benzimidazole type compound is inherently liable to oxidation so that when blended along with crospovidone, it may contain an antioxidant.

[0025] The antioxidant includes, but is not limited to, sodium sulfite, sodium pyrosulfite, vitamin E, rongalite, thioglycerol, sodium thiosulfate, ascorbate and acetyl cysteine.

[0026] Further, the present invention relates to a pharmaceutical preparation comprising a core which comprises at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1, coated with an enteric coating. In the present invention, the term "core" refers to tablets, granules etc. Further, the present invention encompasses a pharmaceutical preparation comprising a core coated with an enteric coating, said core comprising a benzimidazole type compound and at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone laminated therein or coated thereon with spherical granules consisting, as seed granules, of refined white sugar, a mixture of white sugar and starch, or crystalline cellulose etc. The benzimidazole type compound is very unstable under acidic conditions, so when administered, the benzimidazole type compound is decomposed immediately in contact with gastric acid in the stomach, to lose its physiological activity. Accordingly, it should be formed as a pharmaceutical preparation not dissolved in the stomach, that is, a pharmaceutical preparation having a benzimidazole type compound-containing core coated with an enteric substance in order to prevent it from being decomposed in the stomach.

[0027] Further, the present invention relates to a pharmaceutical preparation comprising a core coated with an intermediate coating and further with an enteric coating, said core comprising at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone incorporated into a benzimidazole type compound represented by formula 1. Since the enteric coating is made generally of an acidic substance, its direct contact with the benzimidazole type compound is not preferable. Accordingly, an inert intermediate coating can be provided between the core comprising a benzimidazole type compound and the enteric coating. The term "inert" refers to a substance not adversely affecting the stability of the benzimidazole type compound. The inert intermediate coating may be made of a water-soluble polymer, a water-soluble or water-disintegrating substance or a water-insoluble substance, and specific examples include hydroxypropyl cellulose, hydroxypropylmethyl cellulose, aminoalkyl methaacrylate copolymer E, lactose, mannitol, starch, crystalline cellulose, ethyl cellulose, vinyl acetate etc. When an intermediate coating made of a

water-insoluble substance is applied, water-insoluble fine particles may be mixed in the coating, as disclosed in JP-A 1-290628.

[0028] In the present invention, the above-described pharmaceutical preparation coated with an enteric coating may be coated with a moisture resistant coating. The moisture resistant coating is a coating for inhibiting the passage of steam, and it is functionally a coating which in itself inhibits the transmission of steam or a coating which captures steam in the coating to inhibit the inflow of steam into the inside.

[0029] The moisture resistant coating possesses the function of defending the preparation against invasion of water into the benzimidazole type compound to improve its stability while preventing the cracking and deformation of tablets originating from the swelling of finely ground crospovidone upon moisture absorption.

[0030] The moisture resistant coating may be either a water-soluble coating or a water-insoluble coating, and this coating includes, but is not limited to, a coating consisting of e.g. polyvinyl acetal diethyl aminoacetate, HA Sankyo (a mixture of polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, stearic acid and fumaric acid) and/or polyvinyl alcohol etc., a coating comprising at least one of cellulose derivatives such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose and ethyl cellulose incorporated into it, and/or a sugar coating based on white sugar.

[0031] The moisture resistant coating is useful not only for the benzimidazole type compound but also for a pharmaceutical preparation containing a drug having similar chemical properties. That is, its effect is observed to be significant when it is applied onto a pharmaceutical preparation containing a drug whose decomposition is observed to be accelerated both in the presence of water and upon contact with gastric acid.

[0032] That is, the present invention relates to a pharmaceutical preparation comprising a core which comprises a drug incorporated into it, the drug both being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an enteric coating and further with a moisture resistant coating. Further, an intermediate coating may be coated between the enteric coating and the moisture resistant coating.

[0033] In the present invention, the effect is particularly outstanding where the benzimidazole type compound shown in formula 1 is rabeprazole.

[0034] That is, the present invention relates to a composition comprising sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt thereof.

[0035] Further, the present invention relates to a composition comprising 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt thereof.

[0036] As described above, the crospovidone used is preferably finely ground until its average particle diameter is decreased to several μm to 50 μm. Further, an antioxidant may be added to prevent the influence of trace peroxides contained in crospovidone, as described above. Accordingly, an antioxidant may be incorporated into the composition comprising 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated into rabeprazole or an alkali metal salt thereof.

[0037] The present invention relates further to a pharmaceutical preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an enteric coating.

[0038] The present invention relates further to a pharmaceutical preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an intermediate coating and further with an enteric coating.

[0039] The present invention relates further to a pharmaceutical preparation comprising a core which comprises 1) crospovidone and 2) sodium hydroxide, potassium hydroxide and/or sodium carbonate incorporated preferably into rabeprazole shown in formula 3 or an alkali metal salt, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

[0040] The composition or the pharmaceutical preparation according to the present invention can be produced by any conventionally used processes.

[0041] For example, at least one selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone is incorporated into a benzimidazole type compound or an alkali metal salt thereof, then excipients are added thereto, and the mixture granulated in a dry or wet granulating process, followed by adding a disintegrating agent such as crospovidone as necessary and subsequently tabletting the granules whereby the composition or the pharmaceutical preparation of the invention can be produced. Alternatively, for example, at least one substance selected from sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone is incorporated at high density into a benzimidazole type compound or an alkali metal salt to prepare benzimidazole-containing granules, while placebo granules not containing the benzimidazole type compound are separately prepared, and then both the granules are mixed followed by adding a disintegrating agent such as crospovidone as necessary and subsequently tabletting the granules. As a matter of

course, these processes are non-limiting examples.

[0042] In a concrete example, e.g. 100 g sodium rabeprazole as the benzimidazole type compound, 30 g sodium carbonate and 130 g mannitol are mixed, and hydroxypropyl cellulose dissolved in ethanol is gradually added to the mixture under stirring, followed by granulation, drying and screening through a 24-mesh screen. 30 g crospovidone and 2 g calcium stearate are added thereto, mixed and tabletted whereby tablets each weighing 135 mg can be obtained.

[0043] These tablets are sprayed by using a fluidized-bed granulator with a solution of hydroxypropyl cellulose in ethanol and further with a solution of hydroxypropylmethyl cellulose phthalate or an enteric methaacrylate copolymer in water/ethanol whereby enteric tablets provided with an intermediate coating can be produced.

[0044] According to the present invention, it is possible to stabilize the very unstable benzimidazole type compound. Examples of this effect are shown below.

Experimental Examples

[0045] 50 mg sodium rabeprazole and 450 mg additives shown in the table below were mixed in a mortar.

[0046] The mixture was introduced into a transparent glass vial and stored in a cold place or at 60 °C or 40 °C under 75 % relative humidity for 1 week and their content was determined by high performance liquid chromatography. Assuming that the content of the sample stored in the cold place is 100 %, the degrees of the residual content under the respective conditions are shown in Tables 1 through 3. Further, their coloring changes were visually evaluated. The sodium rabeprazole used was amorphous in Table 1 and crystalline in Tables 2 and 3. In Table 1, low-substituted hydroxypropyl cellulose (expressed as L-HPC) used as a disintegrating agent in addition to amorphous sodium rabeprazole was blended in the control; in Table 2, a sample further incorporating aluminum hydroxide (expressed as $Al(OH)_3$ in the table) i.e. an alkaline inorganic salt used as an antacid agent was used; and in Table 3, a sample incorporating polyvinyl pyrrolidone (expressed as PVP in the table) was used as a binder.

Table 1

Compatibility Test of Sodium Rabeprazole			
		60°C	40°C-75%RH
Control	sodium rabeprazole (amorphous)	99.1	93.9
	sodium rabeprazole + L-HPC	80.4	73.3
The present application	sodium rabeprazole + crospovidone	98.1	90.4
Unit : %			

Table 2

Compatibility Test of (crystalline) Sodium Rabeprazole			
		60°C	40°C-75%RH
Control	sodium rabeprazole (crystalline)	99.8	91.8
	sodium rabeprazole + L-HPC	62.2	75.0
	sodium rabeprazole + $Al(OH)_3$	36.9	26.2
The present application	sodium rabeprazole + crospovidone	93.3	89.5
	sodium rabeprazole + Na_2CO_3	99.1	90.3
	sodium rabeprazole + Arg • Asp	97.5	90.7
Unit : %			

Table 3

Compatibility Test of (Crystalline) Sodium Rabeprazole			
		60°C	40°C-75%RH
Control	sodium rabeprazole (crystalline)	97.3	86.9
	sodium rabeprazole + PVP	89.5	67.7
The present application	sodium rabeprazole + hydroxypropyl cellulose	92.0	86.9
	sodium rabeprazole + Na_2CO_3	93.0	82.8
	sodium rabeprazole + NaOH	91.6	98.8
	sodium rabeprazole + KOH	92.6	96.8
	sodium rabeprazole + Eudragit E	102.4	86.0
	sodium rabeprazole + K_2CO_3	104.5	81.3
Unit : %			

[0047] Any coloring changes of the blended samples according to the present invention were lower than those of the controls. Further, it is evident from the results of content stability in Tables 1 through 3 that the ingredients used in the present invention, that is, sodium carbonate (expressed as Na_2CO_3 in the table), sodium carbonate (expressed as K_2CO_3 in the table), sodium hydroxide (expressed as NaOH in the table), potassium hydroxide (expressed as KOH), aminoalkyl methaacrylate copolymer E (expressed as Eudragit E®), arginine aspartate (expressed as Arg • Asp in the table), hydroxypropyl cellulose and crospovidone stabilize the benzimidazole type compound.

Effect of Sodium Carbonate in Tablets

[0048] Tablets containing different amounts of sodium carbonate, obtained in Examples 4 to 9 shown below, were stored at 40 °C under 75 % relative humidity for 1 week, and the contents of sodium rabeprazole in the tablets as determined by high performance liquid chromatography were shown in Table 4.

Table 4

Stability Evaluation of Tablet Formulations by Wet Granulation						
Formulation	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9
(1week)						
cold place	99.4	99.0	98.7	99.4	99.5	98.9
40°C-75%RH	83.8	85.7	85.1	92.5	92.8	95.5
(1 month)						
cold place	99.7	99.7	99.7	99.7	99.7	99.6
25°C-75%RH	97.8	98.5	98.3	99.2	99.3	99.3
Unit : %						

[0049] Because the stability of the content of sodium rabeprazole in the tablets is improved depending on the amount of sodium carbonate added, the effect of sodium carbonate added in the present invention is evident.

Effect of Crospovidone in Tablets

[0050] Tablets containing different amounts of crospovidone powder, obtained in Examples 10 to 12 shown below,

were stored at 40 °C under 75 % relative humidity for 1 week, and the contents of sodium rabeprazole in the tablets as determined by high performance liquid chromatography were shown in Table 5. The tablets were subject to less coloring change as the amount of the crospovidone powder added was increased.

Table 5

Stability of Crospovidone-Added Tablets by Wet Granulation			
Formulation	Ex.10	Ex.11	Ex.12
(1week)			
cold place	99.7	99.7	99.7
40°C-75%RH	97.8	98.5	98.3
(1month)			
cold place	99.4	99.0	98.7
40°C-75%RH	83.8	85.7	85.1
Unit : %			

[0051] It is evident that the stability of the benzimidazole type compound is improved by adding crospovidone.

Effect of Finely Ground Crospovidone in Tablets

[0052] Tablets containing crospovidone having a different average particle diameter, obtained in Examples 16 to 18 shown below, were stored in a cold place or at 25 °C under 75 % relative humidity for 1 month and then evaluated for their thickness to evaluate the ratio of swelling of the tablets stored at 25 °C under 75 % relative humidity to swelling of the tablets stored in the cold place. The results were that the ratios of swelling of the tablets containing crospovidone having average particle diameters of 51 μm, 12 μm and 6 μm were 1.61, 1.48 and 1.43, respectively.

[0053] The smaller the average of the particle diameter of the crospovidone was, the smaller the ratio of the swelling of the tablets became. Therefore, as crospovidone is made fine powder having a small average particle diameter, the cracking or deformation resulting from the swelling of the tablets is reduced. Accordingly, it is evident that the particle size reduction of crospovidone contributes to improvement of stability of tablets.

Effect of a Moisture Resistant Coating Applied onto Tablets Coated with an Enteric Coating

[0054] Tablets coated with an enteric coating and tablets coated with both an enteric coating and a moisture resistant coating, obtained in Examples 19 to 20 shown below, were stored at 25 °C under 75 % relative humidity for 1 week, and the content of a rabeprazole analogue (impurities) in the tablets was determined by high performance liquid chromatography. The results indicated that the contents of the rabeprazole analogue (impurities) in the tablets coated with an enteric coating and the tablets coated with both an enteric coating and a moisture resistant coating were 2.38 % and 2.23 %, respectively.

[0055] It is evident that the tablets coated with both an enteric coating and a moisture resistant coating possess stability equal to or higher than that of the tablets coated with an enteric coating.

[0056] Placebo tablets obtained in Examples 21 to 23 shown below were stored in a cold place or at 40 °C under 75 % relative humidity for 1 week and then evaluated for their thickness to evaluate the ratio of swelling of the tablets stored at 40 °C under 75 % relative humidity to swelling of the tablets stored in the cold place. The results indicated that the ratios of swelling of the tablets coated with an enteric coating, tablets prepared by coating said enteric coating-coated tablets with a moisture resistant coating, and tablets prepared by coating said enteric coating-coated tablets with a moisture resistant coating consisting of HA (Sankyo) (i.e., a mixture of polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, macrogol and talc) were 1.15, 1.03 and 1.12, respectively.

[0057] Since the degree of swelling of the tablets coated with both an enteric coating and a moisture resistant coating is smaller during storage than that of the tablets coated with an enteric coating only, it is evident that the stability in shape of the tablets is improved.

Effect of an Antioxidant Added to the Portion of a Core Containing the Benzimidazole Type Compound

[0058] Tablets containing a different amount of a peroxide, obtained in Examples 24 to 26 shown below, were measured for the content of a sodium rabeprazole analogue (impurities) by high performance liquid chromatography. The results indicate that the amounts of the initial rabeprazole analogue in the tablets incorporating crospovidone containing 18 ppm, 190 ppm and 310 ppm peroxide were 0.65 %, 0.88 % and 1.13 % respectively, indicating that as the amount of the peroxide in crospovidone is increased, the decomposition of sodium rabeprazole is promoted to increase the amount of the analogue.

[0059] Further, 1 g crospovidone containing 201 ppm peroxide was accurately taken, and sodium sulfite (amounts: 4 levels i.e. no addition, 0.02 %, 0.05 % and 0.10 %) was added thereto and mixed well, and the amount of the peroxide in the mixture was determined according to a test method described in the Japanese Pharmacopoeia. The results indicated that the amounts of the peroxide in the compositions wherein the amounts of sodium sulfite added were none, 0.02 %, 0.05 % and 0.10 %, were 201 ppm, 184 ppm, 108 ppm, and 0 ppm respectively, indicating that as the amount of sodium sulfite added was increased, the amount of the peroxide was reduced.

[0060] From the foregoing, it is evident that the stability of the benzimidazole type compound in a pharmaceutical preparation is improved by adding the antioxidant to the portion of cores in tablets containing the benzimidazole type compound and crospovidone.

Examples

[0061] Hereinafter, the present invention is described more in detail by reference to Examples, which however are not intended to limit the present invention.

Example 1

[0062] 10 g sodium carbonate and 100 g mannitol were added to and mixed with 10 g sodium rabeprazole, and 2.5 g hydroxypropyl cellulose dissolved in ethanol was gradually added to the mixture under stirring to make granules which were dried and screened followed by adding calcium stearate and tabletting to give tablets each weighing 120 mg containing 10 mg sodium rabeprazole.

Example 2

[0063] The tablets obtained in Example 1 were sprayed by using a fluidized-bed granulator with a solution of 10 g hydroxypropylmethyl cellulose phthalate dissolved in a mixed solvent of water and ethanol (2 : 8), to produce enteric tablets.

Example 3

[0064] The tablets obtained in Example 1 were sprayed by using a fluidized-bed granulator with a solution of hydroxypropylmethyl cellulose in ethanol, to produce enteric tablets in the same manner as in Example 2.

Examples 4 to 9

[0065] 0 to 10 g sodium carbonate and 15 to 90 g mannitol were added to and mixed with 10 g sodium rabeprazole, and 0.7 to 2 g hydroxypropyl cellulose dissolved in ethanol was gradually added to the mixture to make granules under stirring in a wet granulation process, thus preparing the granules containing sodium rabeprazole. Separately, 2 g hydroxypropyl cellulose dissolved in ethanol was gradually added to 100 g mannitol to produce granules under stirring in a wet process to prepare placebo granules. Then, the main-drug granules were mixed with the placebo granules, and 5 % crospovidone and a slight amount of magnesium stearate were added thereto in a powdery form and tabletted to give tablets each weighing 100.5 mg containing 10 mg sodium rabeprazole. Each formulation is shown in Table 6.

Table 6

Tablet Formation by Wet Granulation							
	Formulation	Ex.4	Ex.5	Ex.6	Ex.7	Ex.8	Ex.9
Active granule	sodium rabeprazole	10.0	10.0	10.0	10.0	10.0	10.0
	anhydrous sodium carbonate	-	-	-	5.0	5.0	10.0
	mannitol	82.0	30.0	20.0	25.0	15.0	20.0
	hydroxypropyl cellulose	2.0	1.0	0.7	1.0	0.7	1.0
	(sub-total)	94.0	41.0	30.7	41.0	30.7	41.0
Placebo granule	mannitol	-	52.0	62.1	52.0	62.1	52.0
	hydroxypropyl cellulose	-	1.0	1.2	1.0	1.2	1.0
	(sub-total)	0.0	53.0	63.3	53.0	63.3	53.0
Powder added	crospovidone	5.0	5.0	5.0	5.0	5.0	5.0
	magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5
	(sub-total)	6.5	6.5	6.5	6.5	6.5	6.5
total		100.5	100.5	100.5	100.5	100.5	100.5
Unit:mg							

Examples 10 to 12

[0066] Tablets were obtained in the same manner as in Examples 4 to 9 except that the amounts of crospovidone powder added were 3 levels, that is, 0, 2.5, and 5 %. Each formulation is shown in Table 7.

Table 7

Formulation of Crospovidone-Added Tablets by Wet Granulation				
	Formulation	Ex.10	Ex.11	Ex.12
Active granule	sodium rabeprazole (crystalline)	10.0	10.0	10.0
	anhydrous sodium carbonate	5.0	5.0	5.0
	mannitol	25.0	25.0	25.0
	hydroxypropyl cellulose	1.0	1.0	1.0
	(sub-total)	41.0	41.0	41.0
Placebo granule	mannitol	56.9	54.4	52.0
	hydroxypropyl cellulose	1.1	1.1	1.0
	(sub-total)	58.0	55.5	53.0
Powder added	crospovidone	-	2.5	5.0
	magnesium stearate	1.5	1.5	1.5
	(sub-total)	1.5	4.0	6.5
total		100.5	100.5	100.5
Unit:mg				

Examples 13 to 14

[0067] According to the 2 formulations shown in Table 8, 0 to 50 g sodium carbonate, 79.3 to 84.3 g mannitol, 4.2 g crospovidone and 1.5 g magnesium stearate were added to 10 mg sodium rabeprazole, mixed well, and directly tabletted to give tablets each weighing 100 mg containing 10 mg sodium rabeprazole.

Table 8

Tablet Formulation by Direct Tabletting		
Formulation	Ex.13	Ex.14
sodium rabeprazole (crystalline)	10.0	10.0
anhydrous sodium carbonate	-	5.0
mannitol	84.3	79.3
crospovidone	4.2	4.2
magnesium stearate	1.5	1.5
total	100.0	100.0
Unit:mg		

Example 15

[0068] 50 g sodium carbonate and 2 g magnesium stearate were added to 100 g sodium rabeprazole, mixed well to make granules under dry compression granulation process, to prepare main-drug granules. Separately, 76.3 g mannitol was added to and mixed well with 4.2 g crospovidone, and 2.3 g hydroxypropyl cellulose dissolved in ethanol was gradually added thereto to make granules under stirring in a wet process to prepare placebo granules. Then, the main-drug granules were mixed with the placebo granules, and a slight amount of magnesium stearate was added thereto in a powdery form and tabletted to give tablets each weighing 100 mg containing 10 mg sodium rabeprazole as shown in Table 9.

Table 9

Tablet Formulation by Dry Granulation		
	Formulation	Ex.15
Active granule	sodium rabeprazole (crystalline)	10.0
	anhydrous sodium carbonate	5.0
	magnesium stearate	0.2
	(sub-total)	15.2
Placebo granule	mannitol	76.8
	crospovidone	4.2
	hyroxypropyl cellulose	2.3
	(sub-total)	83.3
Powder added	magnesium stearate	1.5
total		100.0
Unit:mg		

Examples 16 to 18

[0069] 527 g crospovidone having a different average particle diameter and 20 g hydroxypropyl cellulose were

mixed with 100 g sodium rabeprazole, and 3 g magnesium stearate was added thereto in a powdery form, followed by tabletting to give tablets each weighing 65 mg containing 10 mg sodium rabeprazole as shown in Table 10. Crospovidone used is a product of BASF Ltd., and its average diameter is 51 μm for Colidone CL™, 12 μm for Colidone CLM™ and 6 μm for a hammer mill-ground product of Colidone CLM™.

Table 10

Formulations Containing Crospovidone having Different Particle Diameters			
Formulation	Ex.16	Ex.17	Ex.18
sodium rabeprazole	10.0	10.0	10.0
crospovidone (colidone CL)	52.7	-	-
crospovidone (colidone CLM)	-	52.7	-
crospovidone (ground product of colidone CLM)	-	-	52.7
hydroxypropyl cellulose	2.0	2.0	2.0
magnesium stearate	0.3	0.3	0.3
(sub-total)	65.0	65.0	65.0
Unit:mg Note: Average diameters Crospovidone (Colidone CL): 51 μm Crospovidone (Colidone CLM): 12 μm Crospovidone (ground product of Colidone CLM): 6 μm			

Examples 19 to 20

[0070] The portion of a core containing sodium rabeprazole was granulated with ethanol and coated with a water-insoluble intermediate coating containing ethyl cellulose, crospovidone and magnesium stearate. Further, the resulting granules were coated with a coating to give tablets coated with an enteric coating or with both an enteric coating and a moisture resistant coating. The formulation is shown in Table 11.

Table 11

Formulation of a Pharmaceutical Preparation Having an Enteric Coating and a Moisture Resistant Coating Applied Thereon			
	Formulation	Ex.19	Ex.20
Core	sodium rabeprazole	10.0	10.0
	mannitol	36.2	36.2
	crospovidone	15.6	15.6
	sodium hydroxide	0.1	0.1
	anhydrous sodium carbonate	5.0	5.0
	hydroxypropyl cellulose	2.0	2.0
	magnesium stearate	1.1	1.1
	(sub-total)	70.0	70.0

Table 11 (continued)

Formulation of a Pharmaceutical Preparation Having an Enteric Coating and a Moisture Resistant Coating Applied Thereon			
	Formulation	Ex.19	Ex.20
Intermediate coating	ethyl cellulose	0.5	0.5
	crospovidone	1.0	1.0
	magnesium stearate	0.1	0.1
	(sub-total)	1.6	1.6
Enteric coating	hydroxypropyl cellulose cellulose phthalate	8.0	8.0
	monoglyceride	0.8	0.8
	talc	0.75	0.75
	titanium oxide	0.4	0.4
	yellow iron oxide	0.05	0.05
	(sub-total)	10.0	10.0
Moisture resistant coating	hydroxypropylmethyl cellulose	-	3.0
	macrogol	-	0.6
	talc	-	1.4
	(sub-total)		5.0
total		81.6	86.6
Unit:mg			

Examples 21 to 23

[0071] As placebo tablets not containing the benzimidazole type compound, tablets having a water-soluble intermediate layer of hydroxypropyl cellulose applied onto the portion of cores therein were prepared. The tablets were coated further with an enteric coating to prepare tablets coated with an enteric coating, and further the enteric coating-coated tablets were sprayed with white sugar or HA (Sankyo) to prepare tablets coated with a moisture resistant coating. The formulation is shown in Table 12.

Table 12

Placebo Formulation				
	Formulation	Ex.21	Ex.22	Ex.23
Core	mannitol	31.8	31.8	31.8
	crospovidone(colidone CLM)	27.7	27.7	27.7
	hydroxypropyl cellulose	5.0	5.0	5.0
	magnesium stearate	0.5	0.5	0.5
	(sub-total)	65.0	65.0	65.0
Intermediate coating	hydroxypropyl cellulose	3.0	3.0	3.0
Enteric coating	hydroxypropylmethyl cellulose phthalate	8.0	8.0	8.0
	monoglyceride	0.8	0.8	0.8
	talc	0.75	0.75	0.75
	titanium oxide	0.4	0.4	0.4
	yellow iron oxide	0.05	0.05	0.05
	(sub-total)	10.0	10.0	10.0
Moisture resistant coating	white sugar	-	10.0	-
	HA (Sankyo)*	-	-	10.0
total		78.0	88.0	88.0
Unit:mg				

Note:
HA (Sankyo)*
A mixture of polyvinyl acetal diethyl aminoacetate, hydroxypropylmethyl cellulose, Macrogol and talc.

Examples 24 to 26

[0072] Tablets containing crospovidone with different contents of sodium rabeprazole and a peroxide, sodium hydroxide and sodium carbonate were obtained by granulation in a wet process, according to the formulation in Table 13.

Table 13

Formulation Containing Crospovidone with Different Contents of Peroxide			
Formulation	Ex.24	Ex.25	Ex.26
sodium rabeprazole	10.0	10.0	10.0
mannitol	36.9	36.9	36.9
crospovidone (INF-10)*1	14.0	-	-
crospovidone (INF-10)*2	-	14.0	-
crospovidone (colidone CLM)*3	-	-	14.0
crospovidone (colidone CL)	14.0	14.0	14.0
sodium hydroxide	0.5	0.5	0.5
anhydrous sodium carbonate	2.5	2.5	2.5
hydroxypropyl cellulose	2.0	2.0	2.0

Table 13 (continued)

Formulation Containing Crospovidone with Different Contents of Peroxide			
Formulation	Ex.24	Ex.25	Ex.26
magnesium stearate	1.1	1.1	1.1
(total)	70.0	70.0	70.0
Unit:mg Note: Crospovidone (INF-10)*1: (peroxide content: 18 ppm) Crospovidone (INF-10)*2: (peroxide content: 190 ppm) Crospovidone (Colidone CLM)*3: (peroxide content: 310 ppm)			

Example 27

[0073] 43.5 g finely ground crospovidone and 6 g hydroxypropyl cellulose were added to 30 g sodium rabeprazole, mixed well, and then a solution of sodium hydroxide in ethanol (solution of 1.5 g sodium hydroxide dissolved in ethanol) was gradually added to the mixture under stirring to make granules, followed by drying and subsequent regulation of the size of granules in a small type speed mill. 3 % crospovidone and 1.6 % magnesium stearate were added to the regulated granules, mixed and tabletted into tablets each weighing 70 mg containing 10 mg sodium rabeprazole.

Example 28

[0074] The tablets obtained in Example 27 were coated by using a fluidized-layer granulator with a hydrous ethanol solution containing hydroxypropyl cellulose and a slight amount of magnesium stearate, to give tablets having 2 mg intermediate coating laminated thereon. Then, the tablets coated with the intermediate coating were sprayed by using a fluidized-layer granulator with a hydrous ethanol solution containing hydroxypropyl cellulose phthalate, monoglyceride, talc and titanium oxide, to give enteric tablets coated with 10 mg enteric coating.

Example 29

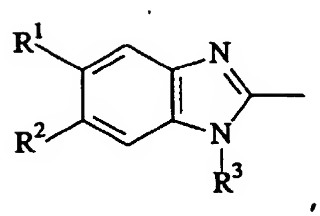
[0075] The enteric tablets obtained in Example 28 were sprayed by using a fluidized-layer granulator with purified water containing hydroxypropylmethyl cellulose, Macrogol 6000™ and talc to give tablets coated with 5 mg moisture resistant coating.

Claims

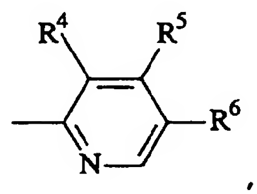
1. A pharmaceutical composition comprising (A) benzimidazole compound represented by the following structural formula (formula 1) or an alkali metal salt thereof and (B) at least one selected from the group consisting of sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methaacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.
Formula 1

$$\mathrm{Het^1{-}\overset{\displaystyle O}{\overset{\|}{S}}{-}CH_2{-}Het^2}$$

In the formula 1, $\mathrm{Het^1}$ is



Het^2 is



R^1 and R^2 are the same as or different from each other and are selected from a hydrogen, a methoxy and a difluoromethoxy, R^3 is selected from a hydrogen and a sodium, R^4, R^5 and R^6 are the same as or different from each other and are selected from hydrogen, methyl, methoxy, methoxypropoxy and trifluoroethoxy.

2. The composition according to Claim 1, wherein the benzimidazole compound is rabeprazole, omeprazole, pantoprazole or lansoprazole.

3. The composition according to Claim 1, which comprises 1 part by weight of (A) and 0.01 to 20 parts by weight of (B).

4. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1 and an enteric coating.

5. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1, an intermediate coating and an enteric coating.

6. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 1, an intermediate coating, an enteric coating and a moisture resistant coating.

7. The composition according to Claim 1, wherein (A) is rabeprazole and an alkali metal salt thereof and (B) is at least one selected from the group consisting of sodium hydroxide, potassium hydroxide and sodium carbonate.

8. The composition according to Claim 1, wherein (A) is rabeprazole or an alkali metal salt thereof and (B) is (1) crospovidone and at least one selected from the group consisting of (2) sodium hydroxide, potassium hydroxide and sodium carbonate.

9. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8 and an enteric coating.

10. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8, an intermediate coating and an enteric coating.

11. A pharmaceutical preparation comprising a core consisting of the composition as claimed in Claim 8, an intermediate coating, an enteric coating and a moisture resistant coating.

12. The composition according to claim 8, which further comprises an antioxidant.

13. The pharmaceutical preparation according to any of Claims 9 to 11, wherein the core further comprises an antioxidant.

14. A pharmaceutical preparation comprising a core which comprises a drug incorporated into it and the drug being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an enteric coating and further with a moisture resistant coating.

15. A pharmaceutical preparation comprising a core which comprises a drug incorporated into it and the drug being accelerated to be decomposed in the presence of water and being chemically unstable in gastric acid, coated with an intermediate coating, further with an enteric coating and then with a moisture resistant coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/02098

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] A61K31/44, A61K9/28, A61K47/02, A61K47/32, A61K47/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] A61K31/44, A61K9/28, A61K47/02, A61K47/32, A61K47/38

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO, 9222284, A1 (Byk Gulden Lomberg Chemische Fabrik GmbH.), 23 December, 1992 (23. 12. 92) & JP, 6-508118, A & EP, 589981, A2	1-6 7-15
X Y	JP, 9-511257, A (Esteve Quimica S.A.), 11 November, 1997 (11. 11. 97) & WO, 9623500, A1 & US, 5626875, A	1-6 7-15
A Y	JP, 9-216847, A (Amano Pharmaceutical Co., Ltd.), 19 August, 1997 (19. 08. 97) (Family: none)	1-13 14, 15
X Y	Drug Development and Industrial Pharmacy, vol. 18, no. 13, p1437-1447, 1992, Teturo Tabata et al., "STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS" Particularly refer to page 1442 ; Table 5	1-6 7-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July, 1999 (12. 07. 99)	21 July, 1999 (21. 07. 99)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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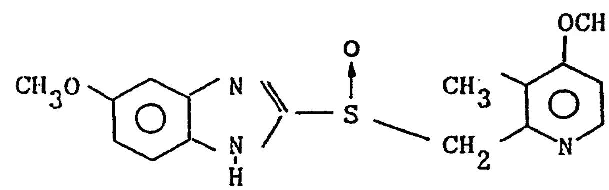
(54) Título: **Procedimiento de obtención de un preparado farmacéutico oral conteniendo omeprazol.**

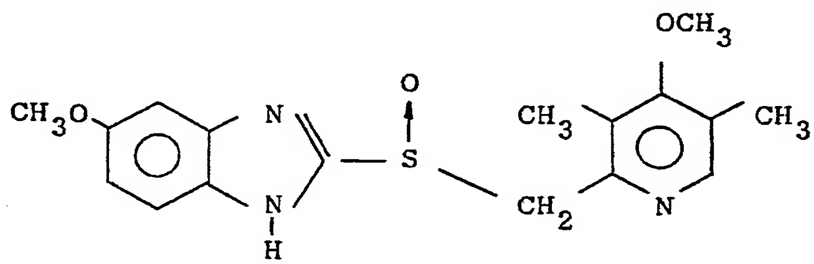
(57) Resumen:
Procedimiento de obtención de un preparado farmacéutico oral conteniendo omeprazol, de fórmula I como ingrediente activo, en el que el omeprazol o una sal alcalina del mismo se mezcla con un primer compuesto básico, formando un núcleo; este es objeto de un primer recubrimiento con una o más capas de un excipiente inerte soluble en agua, junto con un segundo compuesto básico, y posteriormente se efectúa un segundo recubrimiento formado por una cubierta entérica.
El omeprazol es un medicamento muy eficaz para el tratamiento de úlceras gástricas y duodenales y el preparado obtenido le proporciona una buena estabilidad.



(I)

DESCRIPCION

La invención se refiere a un procedimiento de obtención de un preparado farmacéutico oral conteniendo omeprazol, de nombre químico 5-metoxi-2-(((3,5-dimetil-4 -metoxi-2-piridinil)metil)sulfinil)-1H-benzimidazol, de fórmula



(I)

o de alguna de sus sales alcalinas. La síntesis de estos compuestos ha sido descrita por el autor de la presente invención en las patentes españolas núms. 9002764, 9003113 y 9003174.

El omeprazol es un medicamento muy eficaz para el tratamiento de úlceras gástricas y duodenales.

El omeprazol es estable a pH básico, pero se descompone con rapidez a pH neutro o ácido; asimismo, la humedad afecta negativamente a la estabilidad de dicho compuesto. Por tanto, si se suministra el omeprazol por vía oral, éste debe ser protegido del juego gástrico, ácido, a fin de que pueda alcanzar inalterado el intestino delgado, donde tiene lugar la absorción (patente GB -2.189.698-A).

Esta protección se consigue recubriendo el núcleo de omeprazol con una cubierta entérica, insoluble en medio ácido y soluble o fácilmente disgregable en medio neutro o básico. Sin embargo, los compuesto habitualmente empleados para esta finalidad tienen carácter ácido, de modo que el núcleo tiende a descomponerse con el tiempo (patente GB-2.189.698-A).

Este problema se resuelve en parte aumentando la respuesta básica del núcleo, ya sea introduciendo el omeprazol en forma de sal alcalina o alcalinotérrea, o mezclando el omeprazol con un compuesto básico, o bien combinando ambas posibilidades. Con esto se crea un micro -pH básico alrededor de las partículas de omeprazol, aumentando su estabilidad, pero no se elimina el contacto entre el omeprazol y la cubierta entérica ácida.

El hecho de que el núcleo tenga carácter básico plantea una dificultad adicional. La capa externa es parcialmente permeable el agua, de modo que tras la administración del fármaco el agua del tracto digestivo podría llegar el núcleo y disolverse en parte. La solución alcalina así formada atacaría seguidamente la cubierta entérica, provocando eventualmente su destrucción prematura.

Estas dificultades se resuelven interponiendo un primer recubrimiento formado por una o más capas de separación de naturaleza adecada entre el núcleo y la cubierta entérica. Para preparar estas capas se emplea un compuesto o polímero usado para recubrimiento en film que sea inerte, soluble en agua y farmacológicamente aceptable por ejemplo azucar, polietilenglicol o alcohol polivinílico, eventualmente acompañados por un compuesto básico. Este primer recubrimiento o cubierta interna separa el omeprazol de la cubierta externa ácida; además, tiene la función secundaria de actuar como zona tampón de pH, de modo que la acidez estomacal no penetre hasta el núcleo y la basicidad del núcleo no afecte a la capa entérica (patente GB-2.189.698-A).

Desde luego, dichos compuestos básicos citados en los párrafos anteriores deben ser fisiológicamente aceptables. En concreto, para el caso del omeprazol la literatura cita las sales de Na, K, Ca, Mg y Al de ácidos orgánicos o inorgánicos débiles como el ácido cítrico, el fosfórico o el carbónico y los óxidos o hidróxidos de Ca, Mg y Al (patente GB-2.189.698-A).

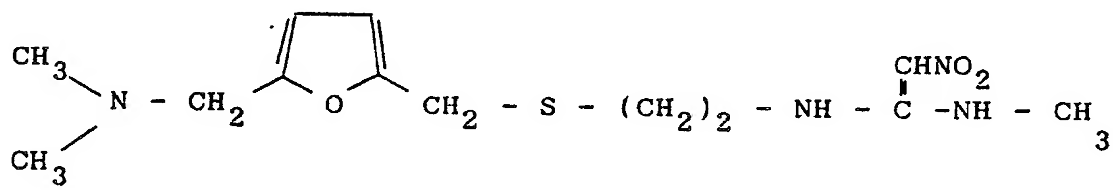
El preparado farmacéutico oral, resultante del procedimiento objeto de la invención y que contiene omeprazol como ingrediente activo, consta: a) de un núcleo que contiene omeprazol o una sal alcalina de

omeprazol mezclados con un primer compuesto básico; b) de un primer recubrimiento de por lo menos una capa intermedia formada por un excipiente y un compuesto básico; y c) de un segundo recubrimiento formado por una cubierta entérica.

La presente invención describe el empleo de nuevos compuestos básicos fisiológicamente aceptables para conseguir la necesaria estabilización del omeprazol presente en el núcleo y aislarlo más efectivamente de la acidez exterior.

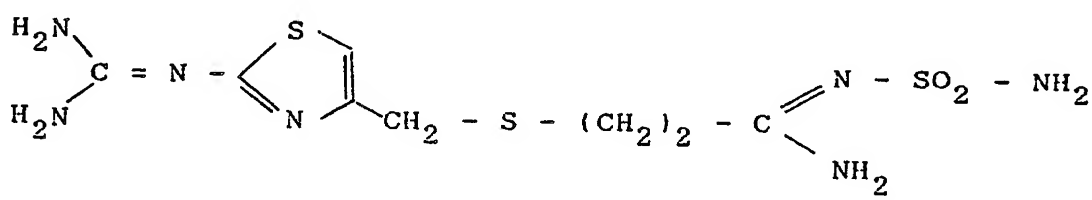
En concreto, dichos compuestos básicas son sales de sodio, potasio, magnesio, calcio, aluminio o dihidroxialuminio de aminoácidos, como la glicocola ($pKa_2 = 9{,}6$), el ácido glutámico ($pka_3 = 9{,}67$) o la lisina ($pka_2 = 8{,}9$, $pka_3 = 10{,}28$), o de un ácido piridincarboxílico, como el ácido nicotínico, o bien son bases orgánicas, como la guanidina (pk 12,5), o una sal de dichas bases con un ácido orgánico o inorgánico débil, por ejemplo carbonato de guanidina, carbonato sódico de guanidina, fosfato de guanidina o fosfato disódico de guanidina, o con un aminoácido como la glicocola o el ácido glutámico. Desde luego, el compuesto debe ser fisiológicamente aceptable.

Para el núcleo también puede utilizarse como compuesto básico la ranitidina, de nombre químico N-(2-(((5-(dimetilamino)metil)-2-furanil)metil)tio)etil)-N'-metil-2-nitro-1,1-etendiamina, de fórmula II



(II)

o la famotidina, de nombre químico 3-(((2-((aminoiminometil) amino)-4-tiazolil)metil)tio) - N - (aminosulfonil) -propanimidamida, de fórmula III



(III)

o bien mezclas de estos productos. Ambos compuestos se emplean, al igual que el omeprazol, para el tratamiento de úlceras gastrointestinales.

La mezcla de compuestos del núcleo se formula como pellets, tabletas o cápsulas de gelatina mediante técnicas farmacéuticas convencionales.

La capa o capas de separación se aplican a los núcleos (pellets o tabletas) aplicando procedimientos de recubrimiento convencionales, empleando una solución del excipiente en agua o en disolventes orgánicos habituales. Como excipiente se emplea un compuesto o polímero inerte soluble en agua usado para recubrimientos en film, por ejemplo hidroxipropilmetilcelulosa, hidroxipropilcelulosa, alcohol polivinílico, polivinilpirrolidona o azúcar. En el caso de las cápsulas de gelatina la propia cápsula sirve como capa de separación.

Por último, la cubierta entérica se aplica sobre los núcleos cubiertos con una o más capas de separación empleando soluciones o suspensiones de polímeros usados normalmente para este tipo de recubrimientos, por ejemplo ftalato acetato de celulosa, ftalato de hidroxipropilmetilcelulosa, copolímero de ácida metacrílico y de metacrilato de metilo o ftalato de polivinilo. En esta cubierta entérica pueden introducirse también dispersantes, colorantes o pigmentos.

En resumen, el procedimiento de la invención está caracterizado porque el omeprazol o una sal alcalina de omeprazol se mezcla con un primer compuesto básico, formando un núcleo el cual es objeto de un primer recubrimiento de por lo menos una capa formada por un excipiente inerte soluble en agua y por un segundo compuesto básico, y de un segundo recubrimiento formado por una cubierta entérica.

Este excipiente puede ser azúcar o alcohol polivinílico y la cubierta entérica está formada por un polímero ácido como el ftalato de celulosa.

Según la invención, dichos compuestos básicos son sales alcalinas, alcalinotérreas, de aluminio o de dihidroxialuminio de aminoácidos como la glicocola o de un ácido piridincarboxílico como el ácido nicotínico, o bien son bases orgánicas como la guanidina o una sal de dichas bases con un ácido orgánico o inorgánico débil o con un aminoácido, por ejemplo fosfato disódico de guanidina o glicocolato de guanidina. Estos compuestos deben ser fisiológicamente aceptables.

Según otra característica de la invención, dicho compuesto básico del núcleo puede ser ranitidina, famotidina o una mezcla de estos compuestos.

Ejemplo 1

Se mezclan 5400 g de manitol en polvo, 260 g de lactosa anhidra, 200 g de hidroxipropilcelulosa y 130 g de celulosa microcristalina y se añade una suspensión de 650 g de omeprazol, 17 g de sulfato sódico de laurilo y 30 g de fosfato disódico de guanidina en 1500 ml de agua. Se agita la masa húmeda hasta que toma la consistencia adecuada y se somete a presión en un aparato para formar pellets. Los pellets se secan y se clasifican en tamaños de partículas adecuados.

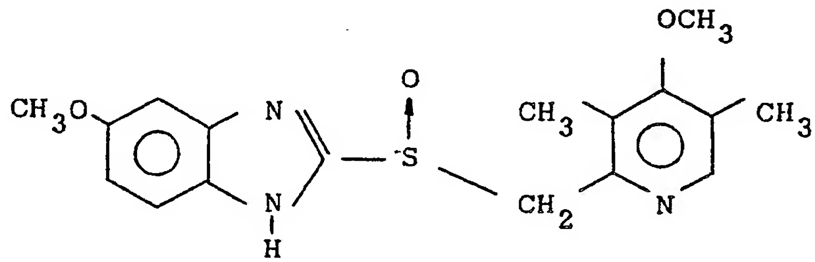
A continuación, 2000 g de estos pellets se rocían en un aparato de lecho fluido con un spray formado por un solución de 80 g de hidroxipropilcelulosa y 20 g de fosfato disódico de guanidina en 1600 ml de agua.

Por último, 150 g de pellets recubiertos como se ha descrito en el párrafo anterior se rocían en un aparato de lecho fluido con un spray formado por una solución de 20 g de ftalato de hidroxipropilemtilcelulosa y 1 g de alcohol cetílico en una mezcla de 180 g de acetona y 80 g de etanol.

Se secan los pellets hasta un contenido de humedad del orden del 0,5%, se clasifican en tamaños y se introducen en una cápsulas de gelatina junto con un compuesto deshidratante.

REIVINDICACIONES

1. Procedimiento de obtención de un preparado farmacéutico oral conteniendo omeprazol, de hombre químico 5 - metoxi - 2 - (((3,5 - dimetil - 4 - metoxi - 2 - piridinil)metil) -sulfinil)-1H-benzimidazol, de fórmula I



(I)

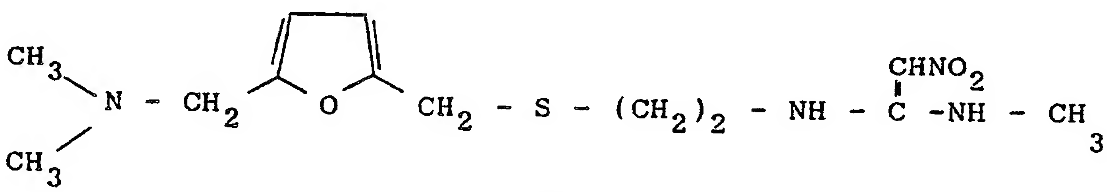
como ingrediente activo, **caracterizado** porque el omeprazol o una sal alcalina de omeprazol se mezcla con un primer compuesto básico, formando un núcleo el cual es objeto

de un primer recubrimiento de por lo menos una capa formada por un excipiente inerte soluble en agua y por un segundo compuesto básico, y

de un segundo recubrimiento formado por un cubierta entérica.

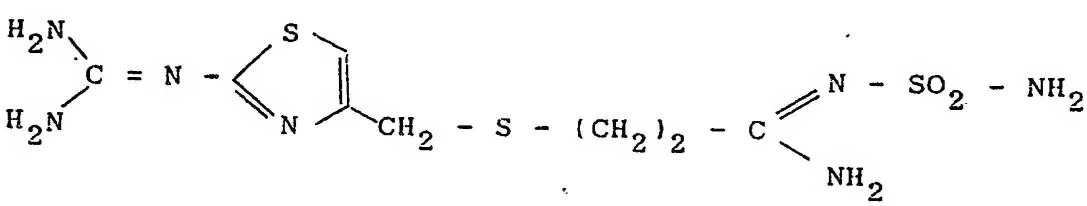
2. Procedimiento según la reivindicación 1, **caracterizado** porque dicha sal alcalina de omeprazol es la sal sódica, potásica o lítica.

3. Procedimiento según la reivindicación 1, **caracterizado** porque dicho primer compuesto básico del núcleo es ranitidina, de nombre químico N-(2-(((5-((dimetilamino) metil)-2-furanil)metil)tio)etil)-N'-metil-2 -nitro-1,1-etendiamina, de fórmula II



(II)

o famotidina, de nombre químico 3-(((2-((aminoiminometil) amino)-4-tiazolil)metil)tio)-N-(aminosulfonil)-propanimidamida, de fórmula III



(III)

o bien mezclas de estos productos.

4. Procedimiento según la reivindicación 1, **caracterizado** porque dicho primero y segundo com-

puesto básico es una sal de sodio, litio, potasio, calcio, magnesio, aluminio o dihidroxialuminio de un aminoácido o de un ácido piridincarboxílico fisiológicamente aceptable.

5. Procedimiento según la reivindicación 4, **caracterizado** porque dicho aminoácido es glicocola, ácido glutámico o lisina.

6. Procedimiento según la reivindicación 1, **caracterizado** porque dicho ácido piridincarboxílico es ácido nicotínico.

7. Procedimiento según la reivindicación 1, **caracterizado** porque dicho primero y segundo compuesto básico es una base orgánica fisiológicamente aceptable o una sal de las mismas con un ácido orgánico o inorgánico débil o con un aminoácido.

8. Procedimiento según la reivindicación 7, **caracterizado** porque dicha base orgánica es la guianidina.

9. Procedimiento según la reivindicación 7, **caracterizado** porque dicha sal de base orgánica es carbonato de guanidina, carbonato sódico de guanidina, fosfato de guanidina, fosfato disódico de guanidina, palmitato de guanidina, estearato de guanidina o glicocolato de guanidina.

10. Procedimiento según una de las reivindicaciones 1 a 9, **caracterizado** porque dicho núcleo posee un pH comprendido entre 7 y 12,5.

11. Procedimiento según la reivindicación 1, **caracterizado** porque dicho excipiente de dicho primer recubrimiento es hidroxipropilmetilcelulosa, hidroxipropilcelulosa, alcohol polivinílico, polivinilpirrolidona o azúcar.

12. Procedimiento según la reivindicación 1, **caracterizado** porque dicha cubierta entérica está formada por ftalato de hidroxipropilmetilcelulosa, ftalato acetato de celulosa, copolímero de ácido metacrílico y de metacrilato de metilo o ftalato acetato de polivinilo, eventualmente en presencia de un dispersante, colorante o pigmento.

(2000円) 特許願

第　　　号

昭和47年4月13日

特許庁長官　殿

1. 発明の名称
有機リン酸エステルの製造法

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明細書

1. 発明の名称　有機リン酸エステルの製造法

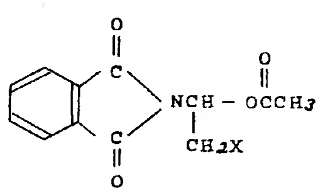
2. 特許請求の範囲

一般式：

$$(RO)_2\overset{Z}{\overset{\|}{P}}-SH \qquad [I]$$

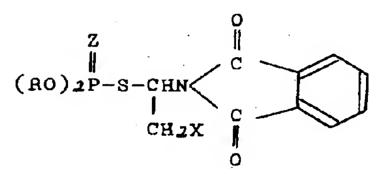
〔式中、Rは炭素数1～3個のアルキル基、Zは酸素原子または硫黄原子を表わす〕で表わされる、O，O－ジアルキルチオリン酸または、ジチオリン酸と、

一般式：


〔II〕

〔式中、Xは塩素原子、または臭素原子を表わす〕で表わされ。N－（1－アセトオキシ－2－ハロエチル）フタールイミドを酸触媒の存在下で反応させることを特徴とする

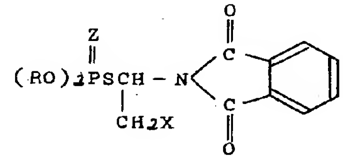
一般式：


〔III〕

〔式中、R，Z，およびXは上記と同じ意義を有する〕で表わされる有機りん酸エステルの製造法。

3. 発明の詳細な説明

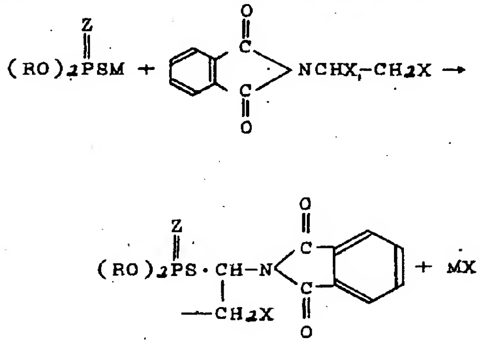
本発明は有機りん酸エステルの製造法に関するものである。更に詳しく謂えば一般式：


〔III〕

〔式中、Rは炭素数1～3個のアルキル基、Zは酸素原子、または硫黄原子、Xは塩素原子または臭素原子を表わす〕で表わされる有機りん酸エステル、特にO，O－ジアルキル－S－（2－ハロ－1－フタールイミドエチル）ホスホロチオエート

および O，O－ジアルキル－S－（2－ハロ・1－フタールイミドエチル）ホスホロジチオエートの製造法に関する。

従来、この有機りん酸エステルは、殺虫効果の優れたものとして知られており、O，O－ジアルキルチオりん酸塩、またはO，O－ジアルキルジチオりん酸塩とN－（1，2－ジハロエチル）フタールイミドとを反応させて製造されているものである。この反応式は次の通りである。



〔式中、Rはアルキル基、Zは酸素原子または硫黄原子、Mはアルカリ金属、アンモニウム、アミン、Xは塩素原子または臭素原子を表わす〕

この場合、出発原料であるN－（1，2－ジハロエチル）フタールイミドは通常N－ビニールフタールイミドをハロゲン化するか、またはN－（2－ハロエチル）フタールイミドをハロゲン化コハク酸イミドと反応させることにより得られるものであるが、前者においては、その収率は低いのみならずN－ビニールフタールイミドを入手することが工業的には極めて不利であり、一方後者においては収率は前者ほどでないとしても、この反応自体は有利な方法とはいえず、更にN－（2－ハロエチル）フタールイミドも前者と同様の理由等によつてN－（1，2－ジハロエチル）フタールイミドを工業的に得ることは困難なことであつた。

かように、この有機りん酸エステルを製造するに当りN－（1，2－ジハロエチル）フタールイミドを出発原料とする前記の反応式による方法では、幾多の隘路があつて、例えば、フタールイミド、または、無水フタール酸からみた目的物たる有機りん酸エステルの収率は極めて低いもので、これを工業的に製造することは容易なことではない。

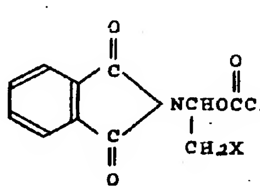
本発明者等は前記有機りん酸エステルの製造法について検討したところ前記の反応式による反応に、よらない、下記に示す新規な反応を見出し、本発明を完成して叙上の欠点を克服した。

即ち、本発明は、一般式：

$$(RO)_2\overset{Z}{\overset{\|}{P}}-SH \qquad 〔I〕$$

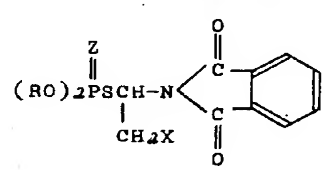
〔式中、Rは炭素数1～3個のアルキル基、Zは酸素原子または硫黄原子を表わす〕で表わされるO，O－ジアルキルチオりん酸またはO，O－ジアルキルジチオりん酸と、

一般式：



〔II〕

〔式中、Xは塩素原子または臭素原子を表わす〕で表わされるN－（1－アセトキシ2－ハロエチル）フタールイミドを酸触媒の存在下で脱酢酸反応させることを特徴とする一般式：



〔III〕

〔式中、R，ZおよびXは上記と同じ意義を有する〕で表わされる有機りん酸エステルの製造法である。

本発明者等の実験によると、出発原料であるN－（1－アセトキシ2－ハロエチル）フタールイミドは、フタールイミドと1，2－ジハロエチルアセテートとの反応により容易に得られるものであつて、本発明に係る製造法は極めて工業的な方法と言うことが出来る。

本発明で使用するN－（1－アセトキシ2－ハロエチル）フタールイミドとしては、

N－（1－アセトキシ2－クロルエチル）フ

タールイミド

N－（1－アセトオキシ－2－ブロモエチル）フタールイミド

等を挙げることが出来る。

一方、他の出発原料であるO，O－ジアルキルチオりん酸またはO，O－ジアルキルジチオりん酸は、3個までの炭素原子数を有するアルキル基をもつ前記の一般式〔I〕で表わされるものである。

次に本発明において反応を行うに当つては、酸触媒を使用することが必要であり、ここに酸触媒というのは、塩酸、硫酸、りん酸などのプロトン酸、塩化亜鉛の如き電子対受容体等であつて通常ルイス酸と呼ばれる酸のことである。それらは一種または、2種以上であつてもよい。

次に反応を行うにあたつての量的関係であるが、O，O－ジアルキルチオりん酸または、O，O－ジアルキルジチオりん酸1モルに対してプロトン酸は0.1～1.5モルであればよいが、その場合プロトン酸の単独使用のときは、一般に若干多く使用し大体0.5～1.5モルであり、特にそれ以上使用しても差支えはない。また、塩化亜鉛の如き電子対受容体と併用して使用するときは、通常0.1～0.2モルが実際的で好ましい。一方他の酸として塩化亜鉛で代表される電子対受容体は前記有機りん酸1モルに対して0.1～1.5モル程度であればよく、就中0.5～1.0モルが実用的で好ましい。本発明の反応を行うに当り、温度範囲は常温から110℃程度まで可能であるが、好ましくは30～70℃で充分である。常温以下の場合は反応速度が遅くなるか、または進行しなくなつてくるからであり、一方、加温すれば反応は速やかに進行するが、有機りん酸の熱安定性から上記の如く自ずと限界がある。

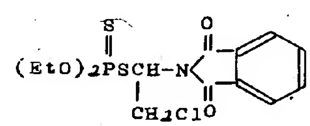
反応時間は、触媒量およびその種類等によつて影響を受けるが、通常1乃至5時間で充分である。この反応は化学量論的な割合で充分行われるが、実際は前記有機りん酸が少過剰にある方が好ましい。次に本発明の反応は特に溶剤を使用しなくとも行われるが、操作上の点から適当な溶剤を用いる方がよい。溶剤としては本発明の反応に不活性なものであれば、いずれも適用可能であり、例えばベンゼン、トルエン、キシレン、クロルベンゼン、四塩化炭素、1，2－二塩化エタン、四塩化エチレン等があげられる。中でも前記一般式〔Ⅱ〕で表わされる有機りん酸エステルの品質上からは、四塩素炭素、四塩化エチレン、1，2＝塩化エタンが好ましいが限定されるものではない。

上記の如き条件で反応を行つたのちは、有機層部分を通常の操作で洗浄し、溶剤を回収することにより、目的物を得ることが出来る。

このように、本発明では、容易に調達出来る前記の化合物を出発原料とするものであり、かつその反応は比較的低温で容易に進行するため多くの場合、目的物の収率は従来に比して高く、しかも高純度の製品が得られる。

次に本発明を実施例をあげて説明する。

以下の実施例で得られる化合物を示せば次の通りである。

1.


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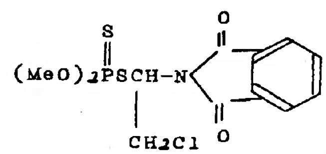

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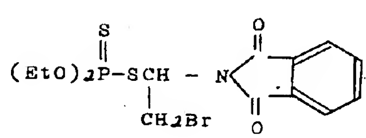

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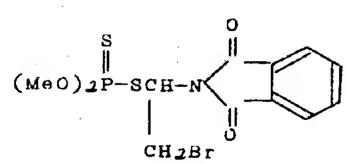
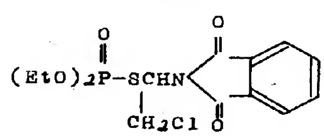
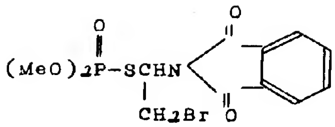
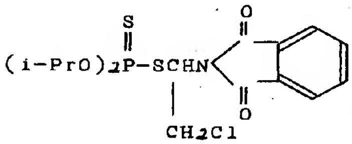
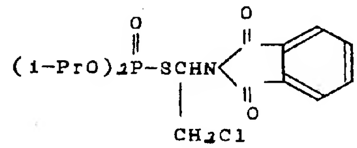


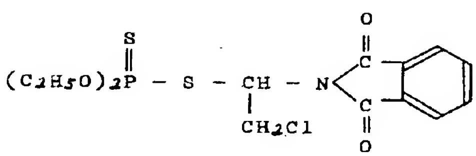
5.


6 

7 

8 

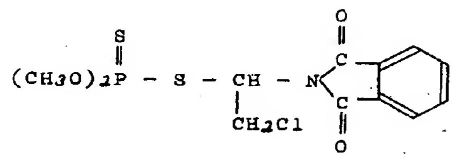
実施例1


の製造

四塩化炭素200mlに、O,O−ジエチルジチオ燐酸19.5g、N−(1−アセトキシ、2−クロロエチル)フタールイミド26.7gを加え、攪拌溶解した後、攪拌しながら濃硫酸9.8gを加え、充分混合し、40℃で4時間加温する。冷却後反応物を、水、炭酸ソーダ水溶液、水で、順次洗浄し、残存する、硫酸、過剰のO,O−ジエチルジチオ燐酸等を除去する。洗滌後、四塩化炭素を留去し、残留物を冷却すると、淡黄色の固体O,O−ジエチル、S−(1−フタルイミド 2−クロロエチル)ホスホロジチオエート37gを得る。このものの純分はガスクロマトグラフイー内標法で93%であつた。エタノールで再結晶すれば融点66℃元素分析値P＝7.86%　Cl＝9.01%　S＝16.10%の結果が得られた。

(計算値　P＝7.86%　Cl＝9.00%
S＝16.28%)

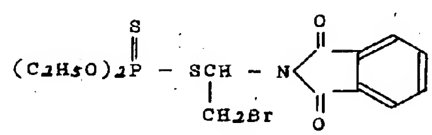
実施例2


の製造

四塩化炭素200mlにO,O−ジメチルジチオ燐酸16.6g、N−(1−アセトキシ 2−クロロエチル)フタールイミド26.7gを加え攪拌溶解した後、攪拌しながら濃硫酸9.8gを加え、充分混合し、40℃で4時間加温する。冷却後反応物を、水、炭酸ソーダ水溶液、水で順次洗滌し、残存する酸性成分を除去する。洗滌後、四塩化炭素を留去すればO,O−ジメチルS−(1−フタルイミド2−クロロエチル)ホスホロジチオエートの黄色粘稠液35gを得る。寒剤で冷却すると淡黄色の固体となる。ガスクロマトグラフイー内標法で純分は88.3%、ベンゼン−ヘキサン系で再結晶すると白色の結晶・融点76.7℃、元素分析でP＝8.39%　Cl＝9.67%　S＝17.3%の結果が得られた。

(計算値P＝8.47%　Cl＝9.69%
S＝17.53%)

実施例3

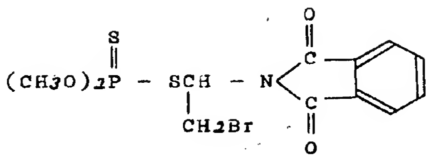

の製造

1,2−ジクロロエタン200mlにO,O−ジエチルジチオ燐酸18.6g N−(1−アセトキシ 2−ブロモエチル)フタールイミド31.2gを加え攪拌混合し、無水塩化亜鉛7g、酢酸10mlを添加して後、混合物を35〜40℃に3時間加温し、反応を終了する。冷却後、反応物を分液ロートに移し、塩酸、炭酸ソーダ、水の順に洗滌して、1,2−ジクロルエタンを留去すると黄褐色の油状液体40gを得る。

ベンゼン−ヘキサン系で再結晶すれば、淡黄色結晶34gを得た。融点73.2〜74.6℃元素分析値は、P＝7.03%　Br＝18.1%
S＝14.5%でありO,O−ジエチル、S−(1フタルイミド2−ブロモエチル)ホスホロジチオ

エートの計算値（P＝7.07％　Br＝18.23％　S＝14.63％）と一値した。

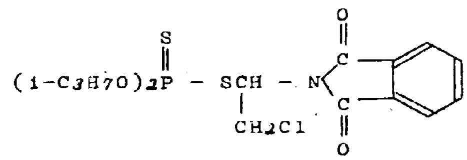
実施例4



の製造

1,2—ジクロロエタン200mlにO,O—ジメチルジチオ燐酸15.8gN—（1—アセトキシ2—ブロモエチル）フタールイミド31.2gを加え攪拌混合し、次いで濃硫酸9.8gを添加し良く攪拌混合しながら、35—40℃に3時間加温する。冷却後、水、炭酸ソーダ、水の順に洗滌し残存酸性成分を除去する。洗滌後、1,2—ジクロロエタンを留去すると茶褐色油状な液体36gを得る。エタノールの少量を加えて寒剤で冷却すれば融点95〜100℃の結晶を得る。再にベンゼン—ヘキサン系で再結晶すると、融点103℃の微色結晶、元素分析値は、P＝7.52％　Br＝19.10％　S＝15.55％でありO,O—ジメチルS—（1—フタルイミド2—ブロモエチル）ホスホロジチオエートの計算値（P＝7.55％　Br＝19.30％　S＝15.63％）と一値した。

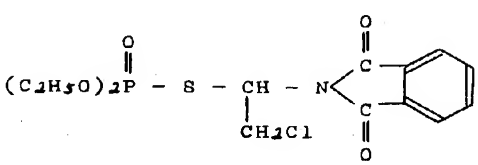
実施例5



の製造

テトラクロロエチレン250mlにO,O—ジイソプロピルジチオ燐酸21.4g、N—（1—アセトキシ 2—クロロエチル）フタールイミド26.7gを加え攪拌混合し、濃硫酸12gを添加し、混合物を攪拌しながら50℃で5時間加温して、反応を完結させる。冷却後、水、2％苛性ソーダ、及び水の順に洗滌した後テトラクロロエチレンを減圧留去すれば、淡橙色油状の液体3.4gを得た。アルミナのカラムクロマトグラフイーで精製し、元素分析した結果、P＝7.40％　Cl＝8.35％　S＝15.21％で、O,O—ジイソプロピルS—（1—フタールイミド2—クロロエチル）ホスホロジチオエートの計算値（P＝7.34％　Cl＝8.40％　S＝15.20％）と一値した。

実施例6



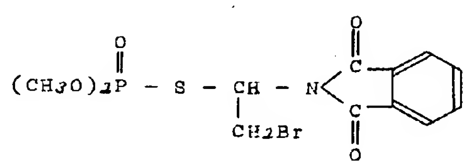
の製造

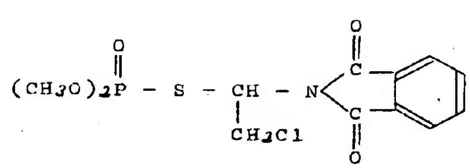
四塩化炭素200mlに、O,O—ジエチルチオ燐酸17.9g、N—（1—アセトキシ 2—クロロエチル）フタールイミド26.7gを加え攪拌混合し、次いで濃硫酸10gを添加し、良く攪拌しながら、45℃に4時間・加温する。冷却後、水、炭酸ソーダ、水の順に洗滌し酸性成分を除去した後、四塩化炭素を留去すると、淡黄色油状の液体O,O—ジエチルS—（1—フタールイミド2—クロロエチル）ホスホロチオエート36.5gを得る。アルミナのカラムクロマトグラフイーで精製し、元素分析値は計算値と一値した。

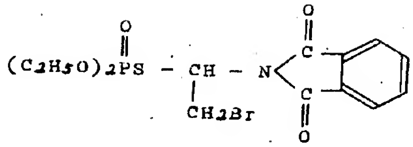
分析値	P＝8.15％	Cl＝9.42％
	S＝8.36％	
計算値	P＝8.20％	Cl＝9.39％
	S＝8.49％	

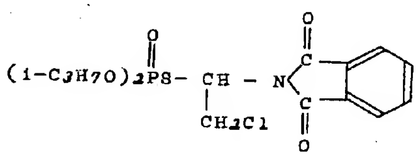
実施例7

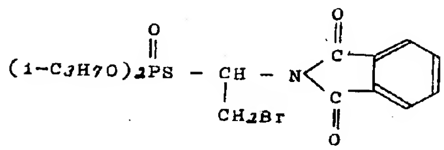
実施例6と同様な方法で、次の化合物が得られることを確認した。

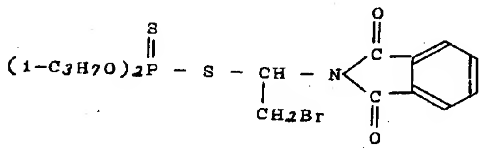












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5. 添附書類の目録

(1) 明　細　書　　1 通
~~(2) 図　　面　　1 通~~
(3) 委　任　状　　1 通
(4) 願書副本　　1 通

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(2,000円)

特　　許　　願　(2)　(後記号ナシ)

昭和47年5月23日

特許庁長官　井　土　武　久　殿

1. 発明の名称

ベンズイミダゾール誘導体の製造法（ユウドウタイ　セイゾウホウ）

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5. 添付書類の目録

(1) 明　細　書　　1通

(2) 委　任　状　　1通

(3) 特許願副本　　1通

特許庁 47.5.25

47 051392

⑲ 日本国特許庁

公開特許公報

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㉒出願日　昭47.(1972) 5.23

審査請求　未請求　　(全5頁)

庁内整理番号	㊾日本分類
6855 44	16 E363
6224 44	30 B4

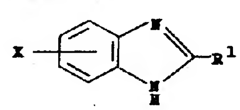
明　細　書

1. 発明の名称

ベンズイミダゾール誘導体の製造法

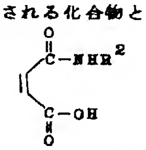
2. 特許請求の範囲

一般式



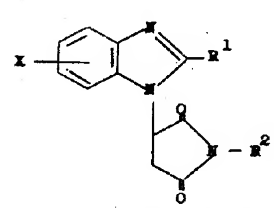
〔式中のXは水素、ハロゲン、低級アルキル、低級アルコキシ、ニトロ基を、R^1は水素、低級アルキル、ヒドロキシ低級アルキル、低級ハロアルキル基を示す。〕

で表わされる化合物と一般式



〔式中のR^2は水素、低級アルキル、低級アルコキシ低級アルキル、シクロアルキル、シクロアルキル低級アルキル、核に置換基を有す、または有しないアリール、アラルキル（置換基はハロゲン、低級アルキル、低級アルコキシ、低級アルコキシカルボニル、低級アルキルチオ、ポリハロ低級アルキル、ニトロ基の中から任意に選ばれる）を示す。〕

で表わされる化合物とを反応させることを特徴とする一般式

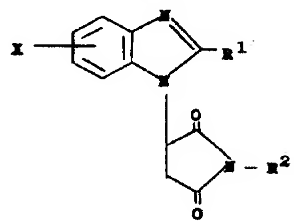


〔式中のX、R^1、R^2は前記のものと同義である。〕

で表わされるベンズイミダゾール誘導体またはその塩の製造法。

3．発明の詳細な説明

本発明は一般式

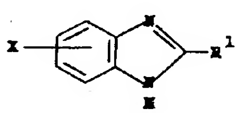


〔I〕

〔式中のXは水素、低級アルキル（メチル、エチル、プロピル、イソプロピル、ブチル、sec－ブチル、tert－ブチル等）、低級アルコキシ（メトキシ、エトキシ）、ハロゲン（フッ素、塩素、臭素等）、ニトロ基を、R^1は水素、低級アルキル、ヒドロキシ低級アルキル（ヒドロキシメチル、2－ヒドロキシエチル等）、低級ハロアルキル（クロルメチル、2－クロルエチル等）を、R^2は水素、低級アルキル、低級アルコキシ低級アルキル（2－メトキシエチル、3－メトキシプロピル等）、シクロアルキル（シクロペンチル、シクロヘキシル、3，3，5－トリメチルシクロヘキシル、シクロドデシル等）、シクロアルキル低級アルキル（シクロヘキシルメチル、2－シクロヘキシルエチル等）、核にハロゲン（フッ素、塩素、臭素等）、低級アルキル、低級アルコキシ、低級アルコキシカルボニル（メトキシカルボニル、エトキシカルボニル等）、低級アルキルチオ（メチルチオ、エチルチオ等）、ポリハロ低級アルキル（トリフルオロメチル等）、ニトロ基等が置換した、または無置換のアリール（フエニル、ナフチル等）、アラルキル（ベンジル、フエネチル等）を示す。〕

で表わされるベンズイミダゾール誘導体またはその塩の製造法に関するものである。

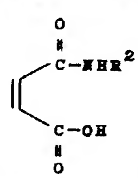
本発明によれば一般式〔I〕で表わされる化合物は一般式



〔II〕

〔式中のX、R^1は前記のものと同義である。〕

で表わされる化合物と一般式



〔III〕

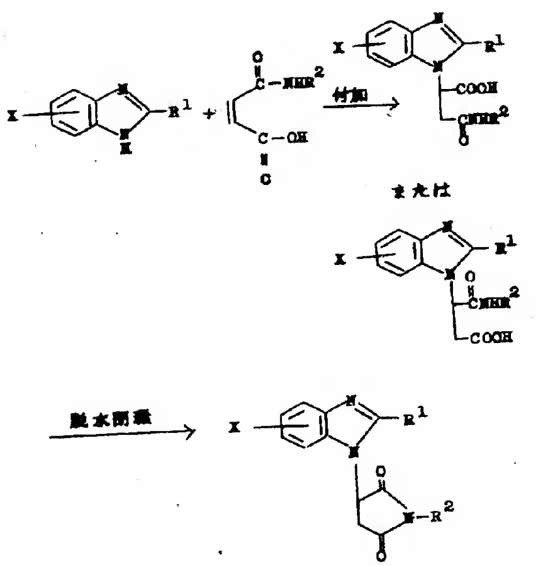
〔式中のR^2は前記のものと同義である。〕

で表わされる化合物とを反応させることにより製造できる。

反応は不活性溶媒中（ジオキサン、テトラヒドロフラン、メタノール、エタノール、プロパノール、ブタノール、アセトン、メチルエチルケトン、メチルブチルケトン、シクロヘキサノン、ジメチルホルムアミド、ジメチルスルホキサイド、ベンゼン、キシレン、酢酸、酢酸エチルおよびそれらの混合物等）、また必要に応じてトリトンB、ナトリウムメトキサイド、酢酸ソーダ、苛性アルカリ等の塩基触媒または酢酸、塩化第二錫等の酸触媒の存在下に70～200℃で数時間～数十時間行なわれるが、有利には溶媒の沸点付近で10～30時間行なうのがよい。さらに必要ならばポリリン酸、無水酢酸等の脱水剤を作用させることもできる。

一般式〔I〕で表わされる本発明の化合物は次のフローシートに従つて製造される。

以下余白



第一段階の付加反応の結果、2種類の異性体が生成すると考えられるが、本発明においてはこの中間体を単離する必要はない。第二段階の脱水閉環反応は、R^2が芳香族基でないときは多くの場合付加反応に続いてかなりの程度まで進行する。

またR^2が芳香族基の場合、あるいは芳香族基でなくても脱水閉環が充分に進行しない場合には、ポリリン酸、無水酢酸等の脱水剤を用いることによって目的を果たすことができる。脱水剤を用いるに際しては、必要に応じて酢酸ソーダ、酢酸カリウム等の促進剤を使用してもよい。反応終了後、得られた化合物は所望により、常法に従って、塩酸塩、硫酸塩、シュウ酸塩、マレイン酸塩、ピクリン酸塩等の有機あるいは無機塩にすることもできる。

かくして得られる本発明化合物は血圧低下作用、中枢抑制作用等を有し、医薬として有用である。

以下に実施例を示して本発明をさらに具体的に説明する。

以下余白

実施例1

ベンズイミダゾール5.9g、マレアミド酸5.8gをジメチルホルムアミド100mlに加え、110～120℃で15時間反応させる。得られた溶液を減圧下に完全濃縮し、残留物にポリリン酸50gを加えて、110～120℃で2時間撹拌する。その後これを室温まで冷却し、氷水300ml中に注ぎ、重曹で中和した後濾過すると5.8gの淡褐色結晶が得られる。これをイソプロピルアルコールから再結すれば融点189～191℃の2―(1―ベンズイミダゾリル)スクシンイミド3.9gが無色結晶として得られる。

実施例2

ベンズイミダゾール11.8g、N―3,3,5―トリメチルシクロヘキシルマレアミド酸23.9gをジオキサン120mlに加え、14時間還流する。得られる褐色透明の溶液を室温まで冷却し、水500ml中に注ぐと油状物が生じる。この油状物を200mlの酢酸エチルで3回抽出する。すべての酢酸エチル層を合わせて、100mlの飽和重曹水で3回、ついで水50mlで1回洗滌し、芒硝にて乾燥後完全濃縮すると21.2gの褐色アメ状物が得られる。これを熱イソプロピルアルコール50mlに溶解し、氷冷すれば融点160～162℃のN―3,3,5―トリメチルシクロヘキシル―2―(1―ベンズイミダゾリル)スクシンイミド9.9gが無色結晶として得られる。

実施例3

ベンズイミダゾール5.9g、N―3,3,5―トリメチルシクロヘキシルマレアミド酸12.0gをジオキサン60mlに加え、14時間還流する。次に無水酢酸20ml、無水酢酸ソーダ1.5gを反

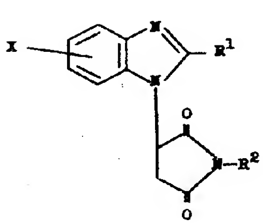
応液に加え、2時間還流する。反応液を室温まで冷却した後氷水300ml中に注ぎ、激しく攪拌しながら重曹で中和する。析出する油状物を100mlの酢酸エチルで3回抽出する。すべての酢酸エチル層を合わせて、これを水100mlで洗った後芒硝で乾燥する。完全濃縮すると14.8gのアメ状物が得られる。40mlのイソプロピルアルコールから再結すれば融点160～162℃のN－3，3，5－トリメチルシクロヘキシル－2－(1－ベンズイミダゾリル)スクシンイミド7.9gが無色結晶として得られる。

実施例4

ベンズイミダゾール5.9g、N－p－クロルフエニルマレアミド酸10.3gをジオキサン70mlに加え、13時間還流する。得られる濃紫色溶液に無水酢酸30ml、無水酢酸ソーダ1.5gを加え、2時間還流する。反応液を室温まで冷却した後氷水300ml中に注ぎ、激しく攪拌しながら重曹で中和する。析出する油状物を100mlの酢酸エチルで3回抽出する。すべての酢酸エチル層を合わせて、これを水100mlで洗った後芒硝で乾燥する。完全濃縮すると13.0gの褐色タール状物が得られるが、これはまもなく固化する。これをジオキサン100mlに溶解し、活性炭で脱色した後、約30mlにまで濃縮し、室温下に放置すれば無色結晶7.2gが得られる。

これをイソプロピルアルコール300mlに溶解し、当量のマレイン酸を加えて氷冷すれば融点145～147℃のN－p－クロルフエニル－2－(1－ベンズイミダゾリル)スクシンイミド・マレイン酸塩6.4gが得られる。

以下同様にして次の化合物が製造できる。



実施例	X	R^1	R^2	塩・融点(℃)
5	H	H	ブチル	塩酸塩　190～192.5
6	H	H	$-(CH_2)_3OCH_3$	塩酸塩・1/4水和物　153～156
7	H	H	シクロドデシル	シユウ酸塩　192～194
8	H	H	フエニル	186～188
9	H	H	o－トリル	シユウ酸塩　193～195
10	H	H	o－クロルフエニル	シユウ酸塩・1/2水和物　188～188.5
11	H	H	p－エトキシフエニル	188～190
12	H	H	m－トリフルオロメチルフエニル	シユウ酸塩　173～174
13	H	H	p－エトキシカルボニルフエニル	181～183.5
14	H	H	p－ニトロフエニル	200～203
15	H	H	1－ナフチル	シユウ酸塩　185～186

実施例	X	R^1	R^2	塩・融点(℃)
16	H	H	ベンジル	塩酸塩　201.5～204.5
17	H	メチル	ブチル	シユウ酸塩　138～143
18	H	H	2,6－キシリル	197～201
19	H	H	p－エトキシフエニル	193～196
20	H	エチル	p－エトキシフエニル	193～194.5
21	H	$-CH_2OH$	p－クロルフエニル	198～200
22	H	$-CH_2OH$	p－エトキシフエニル	シユウ酸塩・1/4水和物　170～171.5
23	5－Cl	H	2,5－ジクロロフエニル	197～198
24	H	$-CH_2Cl$	p－エトキシフエニル	
25	H	H	m－メチルチオフエニル	
26	6－Cl	H	2,5－ジクロロフエニル	
27	5or(6) $-NO_2$	H	p－エトキシフエニル	
28	5or(6) $-OCH_3$	H	p－エトキシフエニル	
29	5or(6) $-CH_3$	H	p－エトキシフエニル	
30	H	H	シクロヘキシルメチル	

6. 前記以外の発明者

住所　大分県中津市１３４５

氏名　小谷　明　司

手続補正書（自発）

昭和　４７年　７　月　日

特許庁　長官　三　宅　幸　夫殿

1. 事件の表示

昭和　４７年特許願第　５１３９２　号

2. 発明の名称

ベンズイミダゾール誘導体の製造法

3. 補正をする者

事件との関係　特許出願人

住　所　大阪市東区平野町３丁目35番地

名　称（６７２）　吉富製薬株式会社

代表者　不　破　　泰

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吉富製薬株式会社内

氏　名（６６３０）　弁理士　高　宮　城　　勝

5. 補正の対象

明細書の発明の詳細な説明の欄

6. 補正の内容

明細書を次の通り補正する。

①　９頁１１行目「・・・・・スクシンイミド」の後に「１／３イソプロピルアルコール和物」を挿入する。

②　１４頁４行目実施例１８のＲ^{1}の欄の「Ｈ」を「メチル」に５行目実施例１９のＲ^{1}の欄の「Ｈ」を「メチル」に９行目実施例２３のＸの欄の「５－Ｃｌ」を「５ or (6)－Ｃｌ」にそれぞれ訂正する。

③　１４頁１２行目（実施例２６）を削除する。

④　１４頁１３行目の「２７」を「２６」に、１４行目の「２８」を「２７」に、１５行目の「29」を「２８」に、１６行目の「３０」を「２９」にそれぞれ訂正する。

以　上

(2,000円)

特　　許　　願（特許法第38条ただし書の規定による特許出願）
(1)

昭和47年6月3日

特許庁長官　井土武久　殿

1. 発明の名称
新規ベンズイミダゾール誘導体の製法
1' 特許請求の範囲に記載された発明の数　2

2. 発明者
住所　大分県中津市大字島田字清堂455−3
氏名　長谷川　充　（ほか1名）

3. 特許出願人
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名称(672)　吉富製薬株式会社
代表者　不破　泰

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住所　大阪市東区平野町3丁目35番地
吉富製薬株式会社内
氏名　弁理士(6630) 高宮城　勝

5. 添付書類の目録
(1) 明細書　1通
(2) 委任状　1通
(3) 特許願副本　1通

方式審査

47 055483

⑲ 日本国特許庁
公開特許公報
⑪特開昭 49−13172
㊸公開日 昭49.(1974) 2. 5
㉑特願昭 47−55483
㉒出願日 昭47.(1972) 6. 3
審査請求　未請求　（全5頁）

庁内整理番号	㉜日本分類
6855 44	16 E363
7306 44	16 E431
6224 44	30 B4

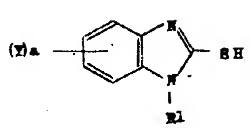
明　細　書

1. 発明の名称

新規ベンズイミダゾール誘導体の製法

2. 特許請求の範囲

(1) 一般式



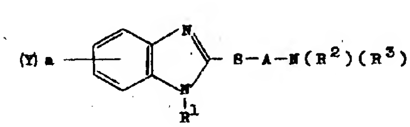
〔式中のR^1は$R-(CH_2)_n-$、$R-CH(OH)(CH_2)_m-$、または$R-CO(CH_2)_m-$（Rは核に置換基を有していてもよい芳香族炭化水素残基または、芳香族複素環残基を、nは1〜2を、mは0〜1を示す。）で表わされる基を、aは1〜4の整数を、a個のYは各々水素、ハロゲン、低級アルキル、低級アルコキシ、ハロ低級アルキル、ポリハロ低級アルキル、ニトロ基を示す。〕

で表わされる化合物と一般式

$$Z-A-N(R^2)(R^3)$$

〔式中のR^2、R^3は同一または異なつて水素、低級アルキル、低級アルケニル、核に置換基を有していてもよいアラルキルを示し、また$N(R^2)(R^3)$は飽和異項環を形成することもできる。Aは炭素数6個までのアルキレンを、Zは活性エステルの酸残基を示す。〕

で表わされる化合物を反応させることを特徴とする一般式

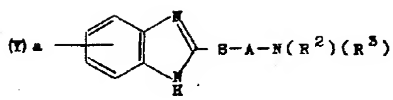


〔式中の(Y)a、R^1、R^2、R^3、Aは前記のものと同義である。〕

で表わされるベンズイミダゾール誘導体またはそ

の塩の製造法。

(2) 一般式



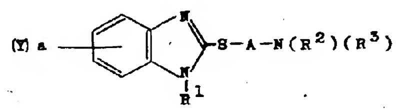
〔式中のR^2，R^3は同一または異なつて水素、低級アルキル、低級アルケニル、核に置換基を有していてもよいアラルキルを示し、また$N(R^2)(R^3)$は飽和異項環を形成することもできる。Aは炭素数6個までのアルキレンを、aは1〜4の整数を、a個のYは各々水素、ハロゲン、低級アルキル、低級アルコキシ、ハロ低級アルキル、ポリハロ低級アルキル、ニトロ基を示す。〕

で表わされる化合物と一般式

$$R^1-Z$$

〔式中のR^1は$R-(CH_2)_n-$、$R-CH(OH)(CH_2)_m-$または$R-CO(CH_2)_m-$（Rは核に置換基を有していてもよい芳香族炭化水素残基または芳香族複素環残基を、nは1〜2を、mは0〜1を示す。）で表わされる基を、Zは活性エステルの酸残基を示す。〕

で表わされる化合物を反応させることを特徴とする一般式

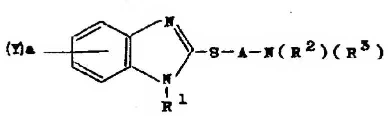


〔式中の(Y)a、R^1、R^2、R^3、Aは前記のものと同義である。〕

で表わされるベンズイミダゾール誘導体またはその塩の製造法。

3. 発明の詳細な説明

本発明は一般式



〔I〕

〔式中のR^1は$R-(CH_2)_n-$、$R-CH(OH)(CH_2)_m-$または$R-CO(CH_2)_m-$｛Rはハロゲン（F，Cl，Br等）、低級アルキル（メチル、エチル、プロピル等）、低級アルコキシ（メトキシ、エトキシ等）、アルキレンジオキシ（メチレンジオキシ等）、ニトロ基等を置換基として有していてもよい芳香族炭化水素残基（フエニル、ナフチル等）または芳香族複素環残基（フリル、チエニル、ピリジル等）を、nは1〜2を、mは0〜1を示す。｝で表わされる基を、R^2，R^3は同一または異なつて水素、低級アルキル、低級アルケニル（ビニル、アリル等）、核に置換基（ハロゲン、低級アルキル、低級アルコキシ、ポリハロ低級アルキル、ニトロ基等）を有していてもよいアラルキルを示し、また$N(R^2)(R^3)$は飽和異項環（ピロリジン、ピペリジン、ピペコリン、モルホリン、チオモルホリン、ピペラジン、メチルピペラジン、ヒドロキシエチルピペラジン、ホモピペラジン等）を形成することもできる。Aは炭素数6個までのアルキレン（エチレン、トリメチレン、プロピレン、2−メチルトリメチレン等）を、aは1〜4の整数を、a個のYは各々水素、ハロゲン、低級アルキル、低級アルコキシ、ポリハロ低級アルキル（トリフルオロメチル等）、ニトロ基を示す。〕

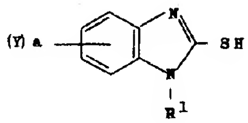
で表わされるベンズイミダゾール誘導体またはその塩（無機酸塩、有機酸塩、第4級アンモニウム塩）の製造法に関するものである。

本発明によれば一般式〔I〕で表わされる化合

物は次の2方法によつて製造できる。

方法①

一般式



〔II〕

〔式中のR^1,(Y)aは前記のものと同義である。〕

で表わされる化合物と一般式

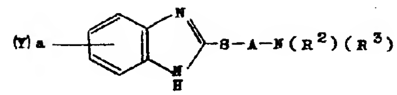
Z—A—N(R^2)(R^3)　〔III〕

〔式中のA，R^2，R^3は前記のものと同義であり、Zは活性エステルの酸残基（ハロゲン、フエニルスルホニルオキシ、p—トリルスルホニルオキシ、メチルスルホニルオキシ等）を示す。〕

で表わされる化合物とを反応させる。

方法②

一般式



〔IV〕

〔式中のR^2，R^3，A，(Y)aは前記のものと同義である。〕

で表わされる化合物と一般式

R^1—Z　〔V〕

〔式中のR^1，Zは前記のものと同義である。〕

で表わされる化合物とを反応させる。反応は不活性溶媒中（ベンゼン、エーテル、テトラヒドロフラン、ジオキサン、アセトン、ジメチルホルムアミド、ジメチルスルホキサイド、酢酸エチル、アルコール、水およびそれらの混合物等）、一般に室温ないし溶媒の沸点の間で行なわれるが、好ましくは50〜100℃である。また必要に応じて脱酸剤（水酸化アルカリ、アルカリアルコキサイド、炭酸アルカリ、有機アミン、水素化ナトリウム、ナトリウムアミド等）の存在下に行なうこともでき、特に方法②の反応ではこれは必須である。

一般式〔I〕で表わされる化合物は所望により、常法に従つて塩酸塩、硫酸塩等の無機酸塩、シユウ酸塩、マレイン酸塩、ピクリン酸塩等の有機酸塩あるいは第4級アンモニウム塩にすることもできる。

かくして得られる本発明化合物は新規であり、強力な抗ヒスタミン作用を有し医薬として有用である。ちなみに、本発明化合物の類似化合物として一般式〔I〕のR^1が低級アルキル、アミノアルキルであるような化合物は公知であるが、その薬理作用については詳しく報じられていない。本発明者等はこの公知化合物についても薬理試験を行なつたが顕著な抗ヒスタミン作用はみられなかつた。

以下に実施例を示して本発明をさらに具体的に説明する。

実施例1.

1—ベンジル—2—メルカプトベンズイミダゾール48gをベンゼン300mlに懸濁させ、これに50%水酸化ナトリウム9.6gを加えて撹拌すると吹立ち、カユ状になる。これにジメチルアミノエチルクロライド塩酸塩23.7gをベンゼン200mlに懸濁させた液を加えて3時間還流する。白色カユ状物は徐々に溶解し、赤黒色溶液になる。これを冷後、洗液が中性になるまで水洗し、希塩酸で抽出する。（塩酸溶液は茶色を示す。）抽出液を炭酸カリで弱アルカリ性にすると油状物が分離するのでこれをクロロホルムで抽出する。この抽出液を芒硝で乾燥後、濃縮すれば1—ベンジル

−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール63gが赤色油状物として得られる。これを塩酸塩にした後エタノールから再結すれば融点197〜198℃の1−ベンジル−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・2塩酸塩が白色結晶として得られる。

実施例2.

1−ベンジル−2−メルカプトベンズイミダゾール12gを95%エタノールに懸濁させた液に水酸化カリウム6.7gを加えると発熱し、濃赤色溶液になる。これにジベンジルアミノエチルクロライド塩酸塩17.8gを50%エタノール100mlに溶かした溶液を加え7時間還流下に攪拌する。冷後、析出する結晶を戸取し、水洗後エタノールから再結すれば融点96〜98℃の1−ベンジル−2−(2−ベンジルアミノエチルチオ)ベンズイミダゾール14.5gが白色針状結晶として得られる。

実施例3.

2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール13.3gを無水ジオキサン70mlに溶解し、これに50%水素化ナトリウム2.9gを加えて6時間加熱する。ついで4−クロロベンジルクロライド10.9gのトルエン溶液を加えて100℃で8時間還流する。冷後、不溶物を除き溶液を完全濃縮する。残留する油状物をベンゼンに溶かし、希水酸化ナトリウム溶液で洗滌、ついで水で洗つた後、希塩酸で抽出する。以下実施例1と同様に処理し、得られる塩酸塩を活性炭処理した後イソプロピルアルコールから再結すれば融点163℃の1−(4−クロロベンジル)−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・2塩酸塩が白色結晶として得られる。

以下同様にして次の化合物が製造できる。

◎ 1−ベンジル−2−(2−ジエチルアミノエチルチオ)−5−トリフルオロメチルベンズイミダゾール・マレイン酸塩 融点147〜148℃

◎ 1−フルフリル−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・修酸塩 融点166〜170℃

◎ 1−フエナシル−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール 融点140〜143℃

◎ 1−(2−ピリジルメチル)−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・修酸塩、融点119〜120℃

◎ 1−(2−ピリジルエチル)−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・修酸塩 融点126〜128℃

◎ 1−(α−ヒドロキシフエネチル)−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・3/2修酸塩・1/2水和物 融点137〜138℃

◎ 1−(2−テエル)−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・2塩酸塩・1/2水和物、(吸湿性) 融点89〜92℃

◎ 1−フエネチル−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・2塩酸塩 融点169℃

◎ 1−ベンジル−2−(2−メチルアミノエチルチオ)ベンズイミダゾール・2塩酸塩・1/2水和物、(吸湿性) 融点166〜169℃

◎ 1−ベンジル−2−(2−ジメチルアミノエチルチオ)ベンズイミダゾール・メトヨーダイド

融点171℃

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(2,000円)

⑲ 日本国特許庁

公開特許公報

⑪特開昭 49－20173
㊸公開日 昭49.(1974) 2.22
㉑特願昭 47－63026
㉒出願日 昭47.(1972) 6.22
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庁内整理番号 6855 44 / 6224 44
㊿日本分類 16 E363 / 30 B4

特許願(1)

昭和47年6月22日

特許庁長官 井 土 武 久 殿

1. 発明の名称
新規なコハク酸誘導体の製造法

2. 発明者
住所 大分県中津市大字島田字清堂455－3
氏名 長谷川 元 (ほか1名)

3. 特許出願人
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名称 (672) 吉富製薬株式会社
代表者 不破 泰

4. 代理人 〒541 電話連絡先:吉富製薬東京支社(特許部上中) TEL270－6531
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5. 添付書類の目録
(1) 明細書 1通
(2) 委任状 1通
(3) 特許願副本 1通

47 063026

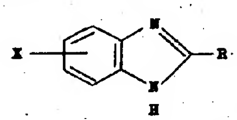
明細書

1. 発明の名称

新規なコハク酸誘導体の製造法

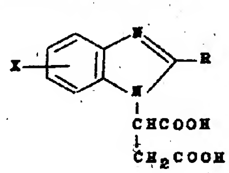
2. 特許請求の範囲

一般式



〔式中Xは水素、ハロゲン、低級アルキル、低級アルコキシ、ニトロ基を、Rは水素、低級アルキル、ヒドロキシ低級アルキル、ハロ低級アルキルを示す。〕

で表わされるベンズイミダゾール誘導体にマレイン酸を反応させることを特徴とする一般式

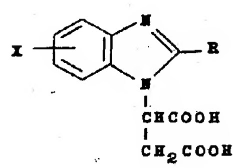


〔式中のX、Rは前記のものと同義である。〕

で表わされるコハク酸誘導体またはその塩の製造法。

3. 発明の詳細な説明

本発明は一般式

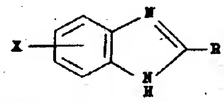


〔I〕

〔式中のXは水素、ハロゲン(F, Cl, Br 等)、低級アルキル(メチル、エチル、ブチル等)、低級アルコキシ(メトキシ、エトキシ等)、ニトロ基を、Rは水素、低級アルキル、ヒドロキシ低級アルキル(ヒドロキシメチル、2－ヒドロキシエチル等)、ハロ低級アルキル(クロルメチル、2－クロルエチル等)を示す。〕

で表わされるコハク酸誘導体またはその塩の製造法に関するものである。

本発明によれば一般式〔I〕で表わされる化合物は一般式



〔II〕

〔式中のX、Rは前記のものと同義である。〕で表わされるベンズイミダゾール誘導体にマレイン酸、より詳しくはマレイン酸の半塩を反応させることにより製造できる。遊離マレイン酸を反応させても単なる付加塩が得られるのみであるが、マレイン酸の半塩を反応させることにより、容易に、かつ好収率で高純度の目的化合物が得られる。この半塩としてはリチウム塩、カリウム塩、ナトリウム塩等の金属塩、トリエチルアンモニウム塩、ピリジニウム塩等の有機アミン塩が適当である。

反応は不活性溶媒中（水、ジメチルホルムアミド、ジメチルスルホキサイド、酢酸、プロピオン酸およびそれらの混合物等）、70～200℃で、好ましくは溶媒の沸点付近で数時間～数百時間行なわれる。反応終了後、目的物は遊離酸、あるいはナトリウム、カリウム、アルミニウム、銀、銅等の金属類や、アンモニア、メチルアミン、ジメチルアミン、トリエチルアミン、ピリジン等のアミン類との半塩、二塩基性塩、または上記塩基類との複塩、錯塩として、あるいはイオン交換樹脂を用いて精製分離してもよい。

かくして得られる本発明の化合物は医薬品としてまたその中間体として有用である。

以下に実施例を示して本発明をさらに具体的に説明する。

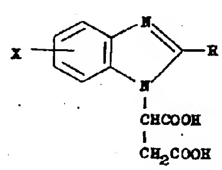
実施例1

ベンズイミダゾール80.0g、マレイン酸78.5g、苛性ソーダ27.1gを水500mlに加え、20時間還流する。得られる無色透明の溶液を氷冷し、濃塩酸55mlを加えると融点228～230℃（分解）の2-（1-ベンズイミダゾリル）コハク酸・1水和物136.2gが粉末状無色結晶として得られる。

実施例2

5-クロルベンズイミダゾール15.3g、マレイン酸11.6g、苛性ソーダ4.0gを水150mlに加え、66時間還流する。得られる淡黄色透明の溶液を室温まで冷却し、濃アンモニア水で弱アルカリ性にすると未反応の5-クロルベンズイミダゾール2.0gが析出する。これを戸去し、母液に濃塩酸を加えてpH2にすれば融点221～222.5℃（分解）の2-（5 or (6)-クロル-1-ベンズイミダゾリル）コハク酸・1/3水和物が得られる。

同様にして以下の化合物が製造できる。



実施例	X	R	融点 (℃)
3	H	メチル	1/2水和物 225～227（分解）
4	H	エチル	211～213（分解）
5	H	$-CH_2OH$	212～214（分解）
6	5 or(6)-NO_2	H	1水和物 147.5～150.5（分解）
7	5 or(6)-OCH_3	H	
8	5 or(6)-CH_3	H	
9	H	$-CH_2Cl$	

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6. 前記以外の発明者

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弐千円
(2,000円)

特　許　願　(2)

昭和47年6月22日

特許庁長官　井土武久　殿

1. 発明の名称

ベンズイミダゾール誘導体の製造法

2. 発明者

住所　大分県中津市大字島田字青堂

氏名　長谷川　元　（ほか1名）

3. 特許出願人

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名称 (672)　吉富製薬株式会社

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5. 添付書類の目録

(1) 明細書　1通

(2) 委任状　1通

(3) 特許願副本　1通

47 063027

⑲ 日本国特許庁

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⑪特開昭　49　20174

㊸公開日　昭49.(1974) 2.22

㉑特願昭　47-63027

㉒出願日　昭47.(1972) 6.22

審査請求　未請求　（全4頁）

庁内整理番号	㊾日本分類
6855 44	16 E363
6224 44	30 B4

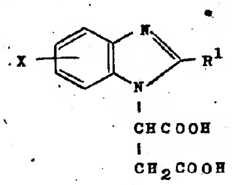
明　細　書

1. 発明の名称

ベンズイミダゾール誘導体の製造法

2. 特許請求の範囲

一般式



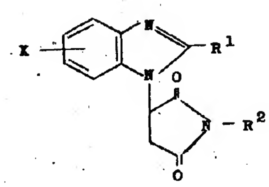
〔式中のXは水素、ハロゲン、低級アルキル、低級アルコキシ、ニトロ基を、R^1は水素、低級アルキル、ヒドロキシ低級アルキル、ハロ低級アルキルを示す。〕

で表わされる化合物と一般式

$$R^2-NH_2$$

〔式中のR^2は水素、低級アルキル、低級アルコキシ低級アルキル、シクロアルキル、核に置換基を有していてもよいアリール、アラルキルを示す。〕

で表わされるアミン類とを反応させることを特徴とする一般式

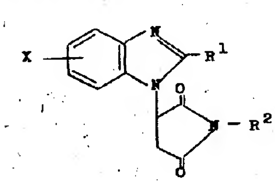


〔式中のX，R^1，R^2は前記のものと同義である。〕

で表わされるベンズイミダゾール誘導体またはその塩の製造法。

3. 発明の詳細な説明

本発明は一般式

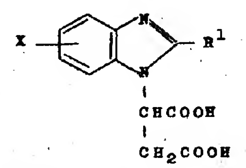


〔I〕

〔式中のXは水素、ハロゲン（F，Cl，Br等）、低級アルキル（メチル、エチル、プロピル、ブチル等）、低級アルコキシ（メトキシ、エトキシ等）、ニトロ基を、R^1は水素、低級アルキル、ヒドロキシ低級アルキル（ヒドロキシメチル、2−ヒドロキシエチル等）、ハロ低級アルキル（クロルメチル、2−クロルエチル等）を、R^2は水素、低級アルキル、低級アルコキシ低級アルキル（2−メトキシメエチル、3−メトキシプロピル等）、シクロアルキル（シクロペンチル、シクロヘキシル、3，3，5−トリメチルシクロヘキシル、シクロドデシル等）、シクロアルキル低級アルキル（シクロヘキシルメチル等）、核に置換基｛ハロゲン、低級アルキル、低級アルコキシ、ニトロ基、ポリハロ低級アルキル（トリフルオロメチル等）、低級アルコキシカルボニル（メトキシカルボニル、エトキシカルボニル等）、低級アルキルチオ（メチルチオ、エチルチオ等）｝を有し、または有しないアリール（フエニル、ナフチル等）、アラルキル（ベンジル、フエネチル等）を示す。〕

で表わされるベンズイミダゾール誘導体の製造法に関するものである。

本発明によれば一般式〔I〕で表わされる化合物は一般式



〔II〕

〔式中のX、R^1は前記のものと同義である。〕

で表わされる化合物と一般式

$$R^2-NH_2 \qquad 〔III〕$$

〔式中のR^2は前記のものと同義である。〕

で表わされるアミン類とを、一般の環状イミド化合物を製造する方法に準じて反応させることにより製造できる。より具体的には、一般式〔II〕のコハク酸の当該アミン塩を、加熱あるいは脱水剤により脱水閉環させる方法や、このコハク酸を、加熱あるいは脱水剤により酸無水物とした後当該アミンとの酸アミドとし、脱水閉環させる方法等である。脱水剤としては塩化チオニル、塩化アセチル、五塩化リン、三塩化リン、ポリリン酸、五酸化リン、無水酢酸、クロル炭酸エステル類等が用いられる。本発明の脱水縮合反応は無溶媒あるいは不活性溶媒中（キシレン、ベンゼン、ジメチルホルムアミド、ジメチルスルホキサイド、テトラヒドロフラン、ジオキサン、酢酸等）、必要に応じ酢酸ソーダ、酢酸カリ等の触媒の存在下に行なわれる。また前記脱水剤を過剰に用いて溶媒を兼ねさせることもできる。

一般式〔I〕で表わされる化合物は所望により塩酸塩、硫酸塩、シユウ酸塩、マレイン酸塩、ピクリン酸塩等の無機あるいは有機酸塩にすることもできる。

かくして得られる本発明の化合物は中枢抑制作用、血圧低下作用を有し、医薬として有用である。

以下に実施例を示して本発明をさらに具体的に説明する。

実施例1.

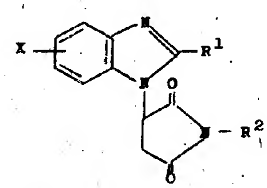
2−（1−ベンズイミダゾリル）コハク酸・1水和物5.0gを塩化アセチル50mlに加え、8時間還流する。反応液を完全濃縮し、氷冷下に2倍当量のアンモニアを含むエタノール溶液を加えた後、エタノールを留去する。残留物にポリリン酸30mlを加え、110〜120℃で2時間攪拌す

る。これを室温まで冷却した後200㎖の氷水中に注ぎ、重曹で中和する。析出する結晶を戸取し、イソプロピルアルコールから再結すれば融点189～191℃の2－(1－ベンズイミダゾリル)スクシンイミド・1／3イソプロピルアルコール水和物1.7gが無色結晶として得られる。

実施例2.

2－(2－メチル－1－ベンズイミダゾリル)コハク酸・1／2水和物2.9g、パラフエネチジン2.7gをよく混和し、1時間150℃に保つ。さらに減圧下(2mmHg～5mmHg)に3時間160～170℃に保つ。これを室温まで冷却した後、残留物を飽和重曹水でよく洗い、ジオキサン150㎖に溶解する。活性炭で処理した後30㎖にまで濃縮し、室温で放置すれば融点193～196℃のN－p－エトキシフエニル－2－(2－メチル－1－ベンズイミダゾリル)スクシンイミド2.0gが無色結晶として得られる。

同様にして以下の化合物が製造できる。



実施例	X	R^1	R^2	塩・融点 (℃)
3	H	H	ブチル	塩酸塩190～1925
4	H	H	$(CH_2)_3OCH_3$	塩酸塩・1/4水和物 153～156
5	H	H	シクロドデシル	シユウ酸塩192～194
6	H	H	3;3,5－トリメチルシクロヘキシル	160～162
7	H	H	フエニル	186～188
8	H	H	o－クロルフエニル	シユウ酸塩・1/2水和物 188～188.5
9	H	H	p－クロルフエニル	マレイン酸塩145～147
10	H	H	o－トリル	シユウ酸塩193～195
11	H	H	p－エトキシフエニル	188～190

実施例	X	R^1	R^2	塩・融点 (℃)
12	H	H	p－エトキシカルボニルフエニル	181～183.5
13	H	H	m－トリフルオロメチルフエニル	シユウ酸塩173～174
14	H	H	p－ニトロフエニル	200～203
15	H	H	1－ナフチル	シユウ酸塩185～186
16	H	H	ベンジル	塩酸塩2015～204.5
17	H	メチル	ブチル	シユウ酸塩138～143
18	H	メチル	2,6－キシリル	197～201
19	H	エチル	p－エトキシフエニル	193～194.5
20	H	$-CH_2OH$	p－クロルフエニル	198～200
21	H	$-CH_2OH$	p－エトキシフエニル	シユウ酸塩・1/4水和物 170～171.5
22	5 or (6) $-Cl$	H	2,5－ジクロルフエニル	197～198
23	H	$-CH_2Cl$	p－エトキシフエニル	
24	H	H	m－メチルチオフエニル	
25	5 or (6) $-NO_2$	H	p－エトキシフエニル	
26	5 or (6) $-OCH_3$	H	p－エトキシフエニル	
27	5 or (6) $-CH_3$	H	p－エトキシフエニル	
28	H	H	シクロヘキシルメチル	

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手 続 補 正 書（方式）

昭和47年10月5日

特許庁 長 官 三 宅 幸 夫 殿

1. 事件の表示
昭和47年特許願第63027号

2. 発明の名称
ベンズイミダゾール誘導体の製造法

3. 補正をする者
事件との関係　特許出願人
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(6630)

5. 補正の対象
願書の発明者の欄

6. 補正命令の日付（発送日）
昭和47年9月26日

7. 補正の内容
願書の発明者の欄の住所「大分県中津市大字島田字清堂」を「大分県中津市大字島田字清堂455—3」とする。

8. 添付書類
特許願　正副各1通

以　上

(2,000円)

特　許　願 (2)

昭和47年6月22日

特許庁長官 井 土 武 久　殿

1. 発明の名称
ベンズイミダゾール誘導体の製造法

2. 発　明　者
住　所　大分県中津市大字島田字清堂455—3
氏　名　長谷川　元　（ほか 1 名）

3. 特許出願人
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5. 添付書類の目録
(1) 明 細 書　1 通
(2) 委 任 状　1 通
(3) 特許願副本　1 通

6. 前記以外の発明者
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特　許　願

昭和47年9月11日

特許庁長官　三宅幸夫　殿

1. 発明の名称（フリガナ）　テングサ　ショリホウホウ
天草の処理方法

2. 発明者
住所（フリガナ）
氏名（フリガナ）　特許出願人に同じ

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5. 添付書類の目録
(1) 明細書　1通
(2) 図面　1通
(3) 委任状　1通
(4) 願書副本　1通

⑲ 日本国特許庁

公開特許公報

⑪特開昭　49－41198
㊸公開日　昭49.(1974) 4.17
㉑特願昭　47－91500
㉒出願日　昭47.(1972) 9.11
審査請求　未請求　　（全3頁）

庁内整理番号	⑤②日本分類
6840 21	8 C1

明　細　書

1. 発明の名称

天草の処理方法

2. 特許請求の範囲

採取後さらしあがつた各種天草をクレープ状に切断し、適当量ミフタスし、これを包装することを特徴とする天草処理方法。

3. 発明の詳細な説明

本発明は寒天製造の原料となる天草の処理方法を提供しようとするものである。

従来天草の処理については採取後、さらして塩分、不純物などを除去し、これらを圧縮したのちむしろなどで包装し、これが寒天製造業者に渡る。寒天製造業者は各種天草を混合し、再度水洗したのち煮つめ寒天を製造している。しかし天草は包装するに際して圧縮してもその性質上一定以上は小さくならず、重量に対して容量が大きく、これが運搬、格納に不便であつた。

本発明はかかる問題を充分解決しようとするもので以下図面を参照しながらその1実施例の詳細を説明する。

採取後水などでさらしたのち、クレープ状に切断する。これを適当容量の袋などに収納包装する。この場合、容量は従来のものにくらべて約70%位小さいものとすることができるから格納運搬に極めて便利である。またこれら切断天草を各種混合したものを煮つめることにより寒天を製造する。なお、この混合は包装前に行つてもよい。

本発明のものは上述のように構成されている

から、

A. 全体の容量を小さくすることができるから格納、運搬などに便である。

B. 寒天製造に関して各種の天草の混合が分量的に正確に行いうる。従つて混合ずみの天草を商品とすることができるから一般家庭での寒天製造が可能である。

C. 寒天製造工程での煮つめる段階で天草の繊維質が細かく切断されているから所謂のりがよく出て製品の分止りがよい。

など、数多くの利点を有する有用な発明と云うべきものである。

特許出願人　加藤千代史

代理人弁理士　川成靖夫

手続補正書

昭和47年11月25日

特許庁長官　三宅幸夫　殿

1. 事件の表示
昭和47年特許願第91500号

2. 発明の名称　天草の処理方法

3. 補正をする者　事件との関係　特許出願人
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フリガナ　カトウチヨシ
氏名　加藤千代史

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氏名　(6917) 弁理士　川成靖

5. 補正命令の日付　昭和　年　月　日(自発)

6. 補正の対称
特許請求の範囲の欄
発明の詳細な説明の欄

7. 補正の内容
別紙のとおり

訂正明細書

1. 発明の名称

天草の処理方法

2. 特許請求の範囲

採取後さらしあがつた各種天草をクレープ状に切断し、粉砕機、又はミキサー機により粉末とし適当量ミツクスし、これを包装することを特徴とする天草処理方法。

3. 発明の詳細な説明

本発明は寒天製造又はところてん製造の原料となる天草の処理方法を提供しようとするものである。

従来天草の処理については採取後さらして塩分、不純物などを除去し、これらを圧縮したのちむしろなどで包装し、これが寒天製造業者に

渡る。寒天製造業者は各種天草を混合し、再度水洗したのち煮つめ寒天、ところてんを製造している。しかし天草は包装するに際して圧縮してもその性質上一定以上は小さくならず、重量に対して容量が大きく、これが運搬、格納に不便であつた。

本発明はかかる問題を充分解決しようとするもので以下図面を参照しながらその1実施例の詳細を説明する。

採取後水などでさらしたのち、クレープ状に切断する。その後粉砕機又はミキサー機により粉末とする。これを適当容量の袋、ダンボールなどに収納包装する。この場合、容量は従来のものに比べて約70%位小さいものにすることができるから格納運搬に極めて便利である。

またこれら粉末天草を各種混合したものを煮つめることにより寒天、ところてんを製造する。なお、この混合は包装前に行つてもよい。

本発明のものは上述のように構成されているから、

A. 全体の容量を小さくすることができるから、格納、運搬に便利である。

B. 寒天、ところてん製造に際して各種の天草の混合が分量的に正確に行いうる。従つて混合ずみの天草を商品とすることができるから一般家庭での寒天、ところてんの製造が可能である。

C. 寒天製造工程での煮つめる段階で天草の繊維質が粉末とされているから所謂のりがよく出て製品の分止りがよい。

など、数多くの利点を有する有用な発明と云うべきものである。

特許出願人　加藤　千代史

代理人弁理士　川成　靖夫

(2,000円)

特　許　願

昭和48年　1月6日

特許庁長官　三　宅　幸　夫殿

1. 発明の名称

工業用殺菌剤組成物

2. 発　明　者

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氏　名　[illegible]　（ほか　3　名）

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住　所　大阪市東区平野町3丁目35番地
吉富製薬株式会社内

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5. 添付書類の目録

(1) 明細書　1通

(2) 委任状　1通

(3) 特許願副本　1通

特許庁
48.1.8

⑲ 日本国特許庁

公開特許公報

⑪特開昭　49－93537

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審査請求　未請求　（全4頁）

庁内整理番号	㊾日本分類
6647 49	30 F371.223
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6258 47	27 A1

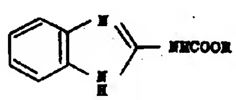
明　細　書

1. 発明の名称

工業用殺菌剤組成物

2. 特許請求の範囲

水およびまたは極性溶媒中に、一般式

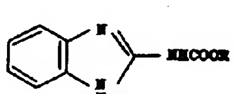


〔式中Rは低級アルキル基を示す。〕

で表わされる化合物およびこれに対して当モルまたは当モル以上のアルカンスルトンを含有させたことを特徴とする工業用殺菌剤組成物。

3. 発明の詳細な説明

一般式


〔I〕

〔式中Rは低級アルキル基を示す。〕

で表わされる2－ベンズイミダゾールカルバミン酸エステル類〔I〕は低毒性と強力な殺カビ性により殺菌剤として重要視されているが、水その他溶媒類に対する溶解性が殆んどないため実用上種々の制約を受けていることは周知の事実である。　1字削除

又2－ベンズイミダゾールカルバミン酸エステル類〔I〕を塩酸、リン酸等の塩に変へ水溶性にすることも試みられている（特公昭45－11319，特公昭47－45494）。しかしこれ等の塩は水及び極性溶媒に対する溶解度が低いことと、水で実用濃度に希釈する場合、結晶の析出を防ぐため過剰の酸の存在が必要である。この様に過剰の酸の存在、特に無機酸の存在は工業用の使用に際して種々の不利な点がある。

本発明者等はこれらの欠点を改良し工業用殺菌

剤としての適応性を広げるため種々検討の結果、2−ベンズイミダゾールカルバミン酸エステル類〔I〕をアルカンスルトン（1，3−プロパンスルトン、1，4−ブタンスルトンなど）と共に、水およびまたはアルコール類またはその他の極性溶媒中で混和することにより水及びこれら溶媒類に易溶であり、特に水には、極めて溶け易く、且つこれらの溶液を多量の水で希釈しても長期間結晶が分離析出しないこと、更に本発明の液組成物が対応する原料の2−ベンズイミダゾールカルバミン酸エステルに比較して殺菌効果が増強されることも見い出し、本発明を完成した。

本発明組成物で用いるアルカンスルトン、たとえばプロパンスルトンは水溶媒中では3−ヒドロキシプロパンスルホン酸を、またアルコール溶媒中ではアルコキシプロパンスルホン酸を生成するが、いずれの場合でも溶解性の優れた組成物が得られる。

本発明の液組成物の溶媒として、水が最も適しているが、ケトン類、メタノール、エタノール等 1字訂正
のアルコール類、エチレングリコール、ジエチレングリコール、分子量約400までのポリエチレングリコール、プロピレングリコール等のグリコール類、その他グリセリン、ジメチルホルムアミド、テトラヒドロフラン等も使用できる。活性成分は通常液組成物の約1〜50％まで含まれる。

本発明の液組成物は調整剤として香料等添加物を水又は油中に容易に分散、溶解し得るようにするために一種又は2種以上の界面活性剤を含ませることができる。ここで云う界面活性剤には一般に使用されている湿潤剤、分散剤、浸透剤、懸濁剤、乳化剤等を含む。界面活性剤として陰イオン性、陽イオン性、非イオン性のものを使用出来るが、特に非イオン性の型のものが好ましい。本発明の液組成物中の界面活性剤の量は通常10％以下の場合が多いが、非イオン性の型の場合50％使用することもある。本発明の液組成物に最も適した界面活性剤として、ポリオキシエチレンアルキルエーテル、ポリオキシエチレンアルキルフェノールエーテル、ソルビタン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、ポリオキシエチレンアルキルアミン等があげられる。その他ベタイン類、アルキルナフタリンスルホネート、縮合ナフタリンスルホネート、リグニン誘導体、ポリオキシエチレンスルホネート、硫酸化アミン及びアミド類、グリセロールエステル類、硫酸化エトキシアルキルフェノール類、スルホコハク酸、アルキルベンゼンスルホネート類等がある。

本発明の液組成物に適当な香料を添加することにより更に商品価値を付与することができる。通常香料は0.5％以下で使用される。この場合前記界面活性剤を組み合わせ使用することにより乳化することなく透明な液組成物を得ることができる。又所望により乳化剤組成物にすることもできる。

以下余白

本発明の該組成物は一般に使用されている工業用殺菌剤、殺細菌剤を含むことが出来る。次に該組成物に添加し得る殺菌剤としては、2－(4－チアゾリル)－ベンズイミダゾール、2－メルカプトピリジン－N－オキシド、トリオキサン、パラホルム、ホルマリン、2－メルカプトベンゾチアゾール、チオシアノ酢酸エステル類、ハロゲノ酢酸エステル類、サリチル酸誘導体類、p－オキシ安息香酸エステル類、ニトロフラン誘導体類、第4級アンモニウム塩類、有機スズ化合物類、メチレンビスチオシアネート、クレゾール及びハロゲン置換フエノール類等があげられる。上記殺菌剤を組合わせ併用することにより本発明組成物の適用範囲が広くなり、予期されなかつた効果をもたらす。又本発明の組成物は殺菌、殺虫剤等と組合わせても使用することができる。

本発明の組成物及び前記の調整剤、殺菌剤等との組合わせた組成物の用途としては、冷却水系、プール、紙パルプ製造所等のスリム剤として使用できる。更に、織物の防腐剤、切削油等金属加工油、水性エマルジョン液の防腐剤、水性ペイント等塗料用防腐剤、石ケン等衛生材料の防腐剤、水性なめし液、生皮処理剤の防腐剤、木材及び木製品、紙製品の防腐保存剤等工業用上及び一般的な分野において使用することができる。

次表は本発明の組成物の代表的な用途及び標準的な使用態様を例示するものである。

以　下　余　白

用　途　例	本発明組成物の活性成分濃度 (ppm)	使　用　態　様
冷却水系スリム剤	10～　1000	直接添加
遊泳プールの消毒剤	1～　100	直接添加
製紙工程のスリム剤	10～　10000	直接添加
織物の防腐保存剤	5～　5000	直接添加
石ケンの殺菌剤	100～　5000	直接添加
金属加工油の防腐剤	10～　5000	乳化剤型、他に防錆剤
塗料の防腐剤	100～　10000	乳剤処方
木材等木製品の防腐保存剤	10～　5000	直接噴霧、浸漬、加圧注入、塗布
レザーの防腐剤	10～　1000	浸漬又はタンニン液等に直接添加も出来る
一般的防腐剤として	1～　100000	直接添加

実施例 1.

2－ベンズイミダゾール

カルバミン酸メチルエステル　　10%

プロパンスルトン　　10%

エチレングリコール　　80%

実施例 2.

2－ベンズイミダゾール

カルバミン酸メチルエステル　　10%

プロパンスルトン　　10%

水　　80%

前記組成液はいずれも溶解は完全であり、3ケ月以上放置しても結晶の分離析出する傾向はなかつた。また50～1000倍の水で希釈しても結晶の析出は起らず、一般に行なわれている様に酸性の水で希釈する必要はなかつた。

次に実施例1、2の組成物の抗菌力について次表に示す。

最少発育阻止濃度　　mcg/ml

供試菌＼実施例	1	2	対照
アスペルギス・ニガー	1	1	4
ペニシリウム・シトリヌム	0.06	0.06	0.5
アスペルギルス・フラバス	1	2	4

対照：2－ベンズイミダゾールカルバミン酸メチルエステル

培養条件：ツアペック培地、28℃、7日

組成物の抗菌力は原体に換算。

代理人　弁理士　高宮城　勝

6. 前記以外の発明者

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氏　名　松　岡　　晋

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氏　名　松　尾　　誠

⑲ 日本国特許庁

公開特許公報

⑪特開昭 49－95997

㊸公開日 昭49.(1974) 9.11

㉑特願昭 48－10463

㉒出願日 昭48.(1973) 1.24

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庁内整理番号	㊾日本分類
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6647 49	30 F371.222
7167 49	30 F932

(2,000円) 特許

特　　許　　願 (2) (後記号ナシ)

昭和48年1月24日

特許庁長官　三宅幸夫　殿

1. 発明の名称

新規なチアゾロベンズイミダゾール誘導体の製造法

2. 発明者

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代表者　不破　泰

4. 代理人 〒541

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氏名　弁理士(6630) 高宮城　勝

5. 添付書類の目録

(1) 明細書　1通

(2) 委任状　1通

(3) 特許願副本　1通

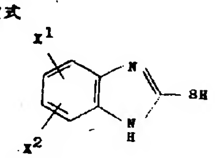
明　細　書

1. 発明の名称

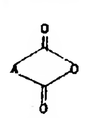
新規なチアゾロベンズイミダゾール誘導体の製造法

2. 特許請求の範囲

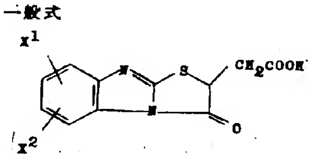
一般式



で表わされる2－メルカプトベンズイミダゾール化合物と一般式



で表わされる酸無水物を反応させることを特徴とする一般式

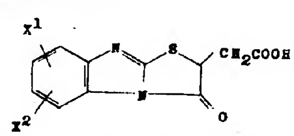


で表わされるチアゾロベンズイミダゾール誘導体の製造法。

上記式中 X^1，X^2 はそれぞれ水素、ハロゲン、低級アルキルまたは低級アルコキシを示し、Aは $-CH=CH-$ または $-CHY-CH_2-$ を示し、ここでYは活性基である。

3. 発明の詳細な説明

本発明は一般式

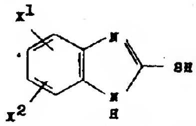


(I)

〔式中 X^1，X^2 はそれぞれ水素、ハロゲン(フッ素、塩素、臭素、ヨウ素)、低級アルキル(メチル、エチルなど)または低級アルコキシ(メトキシ、エトキシなど)を示す。〕

で表わされる新規なチアゾロベンズイミダゾール誘導体の製造法に関する。

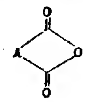
本発明方法によれば、一般式（Ｉ）の化合物は、一般式



（II）

〔式中X^1，X^2は前述のとおり〕

で表わされる２－メルカプトベンズイミダゾール化合物と一般式



（III）

〔式中Ａは$-CH=CH-$または$-CHY-CH_2-$を示し、ここでＹはハロゲン、メチルスルホニルオキシ、ｐ－トリルスルホニルオキシなどの活性基を示す。〕で表わされる酸無水物を反応させることにより製造される。

反応は無溶媒あるいは不活性溶媒（ジオキサン、テトラヒドロフラン、ジエチルエーテル、エチレングリコールジメチルエーテル、ジエチレングリコールジメチルエーテル等のエーテル類、ジメチルホルムアミド、ジメチルアセトアミド、ヘキサメチルホスホロアミド等のアミド類、アセトン、メチルエチルケトン、メチルイソブチルケトン、シクロヘキサノン等のケトン類、酢酸エチル、酢酸ブチル等のエステル類、ギ酸、酢酸、酪酸等のカルボン酸類、リン酸、ポリリン酸、ベンゼン、トルエン、キシレン、クメン、リグロイン等の炭化水素類、クロロホルム、四塩化炭素、ジクロルエタン等のハロゲン化炭化水素類等またはこれらの混合溶媒）中で行なわれる。

反応に際しては、ナトリウムメチラート、カリウムエチラート、カ性ソーダ、カ性カリ、炭酸カリ、炭酸ソーダ、重炭酸カリ、重炭酸ソーダ、重炭酸カルシウム、トリエチルアミン、ピリジン、キノリン、N－メチルモルホリン等の脱酸剤を用いてもよく、またメルカプトベンズイミダゾールをあらかじめ金属塩（ソーダ塩、カリウム塩、リチウム塩、銀塩、銅塩等）として、反応に供してもよい。反応温度は室温から１５０℃付近で、反応時間は数時間から数十時間程度である。

得られる化合物は必要に応じて、ナトリウム、カリウム、銀、銅、カルシウム、バリウム、トリメチルアミン、ピリジン、キノリン等との有機塩、無機塩として単離精製しても良い。

かくして得られる化合物（Ｉ）は植物生長調節作用を有し、農薬として有用である。

以下に実施例を示して、本発明を具体的に説明するが、本発明はこれらのみに限定されるものではない。

実施例１.

２－カルボキシメチル－３－オキソ－２，３－ジヒドロ－チアゾロ〔３，２－ａ〕ベンズイミダゾールの製造

方法１.

２－メルカプトベンズイミダゾール３０ｇ、無水マレイン酸１９.６ｇをジオキサン１００㎖に加え、２４時間還流した。反応液を室温に冷却すると、黄色結晶２８.０ｇを得た。沪液を水１ℓに注ぐと、さらに１３.０ｇの結晶を得た。両結晶を合せ、酢酸より再結晶すると、融点２０７～２０９℃（分解）〔濃褐色の固体に変化〕を示す表題化合物２９.１ｇを黄色結晶性粉末として得た。

方法２.

２－メルカプトベンズイミダゾール１０.０ｇをジメチルホルムアミド２００㎖に溶解し、かくはん下に、無水マレイン酸６.６ｇを含むジメチルホ

ルムアミド溶液80㎖を2時間を要して滴下し、40時間かくはんした。淡褐色透明の反応液を濃縮し、得られた褐色結晶を酢酸より分別結晶すると、原料2ーメルカプトベンズイミダゾール4.0gと表題化合物2.2gを得た。

方法3

2ーメルカプトベンズイミダゾール3.0g、2ーブロモコハク酸無水物3.6g、炭酸カリ2.9gをジオキサン100㎖に加え、60時間かくはん還流した。熱時不溶物を沪去し、沪液を室温まで冷却した後、水1ℓに注ぎ、析出する結晶を酢酸から再結晶すると、表題化合物1.6gを得た。

方法4

2ーメルカプトベンズイミダゾール3.0g、無水マレイン酸3.0gをよく混和し、封管中で120〜140℃に6時間保つた。得られた固型物を酢酸から再結晶すると、表題化合物1.3gを得た。

前記実施例と同様な方法により、次の化合物が製造される。

◎ 2ーカルボキシメチルー6ー(または7ー)クロロー3ーオキソー2,3ージヒドローチアゾロ〔3,2ーa〕ベンズイミダゾール、融点176〜178℃(分解)

◎ 2ーカルボキシメチルー6,7ージメトキシー3ーオキソー2,3ージヒドローチアゾロ〔3,2ーa〕ベンズイミダゾール、融点220℃以上

◎ 2ーカルボキシメチルー6ー(または7ー)メチルー3ーオキソー2,3ージヒドローチアゾロ〔3,2ーa〕ベンズイミダゾール、

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手続補正書

昭和48年4月18日

特許庁 長官 三宅幸夫 殿

1. 事件の表示

昭和48年特許願第10463号

2. 発明の名称

新規なチアゾロベンズイミダゾール誘導体の製造法

3. 補正をする者

事件との関係 特許出願人

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5. 補正の対象

明細書の発明の詳細な説明の欄

6. 補正の内容

明細書第8頁14行目の「ベンズイミダゾール、」の次に「融点173～175℃(分解)」を挿入する。

以　上